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THE ENDOCRINE TREATMENT OF PAGET'S DISEASE*

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In 1876, Sir James Paget described the disease which he named osteitis deformans but which has also since become known as Paget's Disease of the bones, to distinguish it from Paget's Disease of the nipple. He based his first description of the disease in a paper read before the Royal Medical and Chirurgical Society of London on five cases, two being his own cases, the first of which he saw twenty years before he described it, the other three having been described by others, one of them being described by Wilks, in 1869.

Paget's first patient suffered first with aching pains in the thighs and legs, chiefly after active exercise. After about a year he noticed that his left thigh was misshapen. This was followed by an enlargement of the right side of the skull. The spine slowly became curved and rigid—and the habitual posture and gait were made peculiar, the whole effect suggesting the Neanderthal Man. The upper limbs remained perfect and there was no disturbance of general health. Hemorrhages and thromboses developed in the retinal vessels and deafness also. The urine contained frequent deposits of lithates. Autopsy showed a spongy hyperostosis of the bones, due to excessive hydration of them, with loss of calcium phosphate. Paget reported altogether, in three classic papers, one published in 1876, one in 1882 and one in 1889, 23 personally observed cases.

NATURAL HISTORY

As the name indicates, the outstanding development of the natural history of this disease is a deformation of the skeleton, accompanied by various subjective complaints and symptoms. The end product of the deformation is the spectacle of an artificially dwarfed-looking old man, simian in attitude, with the bones of the legs markedly bowed forward and outward, a sunk and shrunken spinal column and chest, thickened collar bones, arms descending to the knees or lower, all in contrast with the disproportionally large intellectual-looking head. The subjects die of general weakness and circulatory deficiency.

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The onset of the condition is slow and insidious. For many months or years there may be only vague "rheumatic" pains in the extremities which are not to be distinguished by ordinary standards from the pains of the classical rheumatic conditions. Gradually objective disturbances occur, most commonly in the bones, consisting in a bowing and shortening, so that his friends seem to the patient to be growing taller, while he himself is growing shorter—or in an increase in the size of the head, necessitating the buying of larger and larger sized hats—or by the sudden occurrence of pathological fractures. The trapezoid face, produced by enlargement of the skull without enlargement of the facial bones may be compared with the diamond-shaped abdomen, with the four angles made by the ensiform cartilage, the symphysis pubis and the two ilio-costal angles approximated because of shortening of the spine. Some reporters have asserted that the bones of the pelvis are always involved and are always the first involved, asserting this in spite of the description of a localized or mono-osteitic form of the disease in which it is apparently limited to one bone, such as the tibia or femur. At any rate, the orthopedist is often the first one to see these patients because they present complaints pointing to the sacro-iliac region. When the bones of the head are severely diseased, the narrowing of the neural foramina may produce symptoms referable to the cranial nerves, while involvement of the vertebrae may cause symptoms of compression of the cord. One form of the disease I have not seen referred to may be described as the circulatory form—the symptoms are primarily cardiac and circulatory such as fibrillation of the heart. One such patient was treated for several years for the heart symptoms. When the diagnosis of Paget's Disease was made, the heart symptoms yielded to the general treatment, no special cardiac remedy being given.

FREQUENCY OF THE DISEASE

Until the more general use of the x-ray in the diagnosis of obscure cases—which may be said to begin with 1916-1917—Paget's Disease was considered an extremely rare disease. Thus Osler in 1912 stated that the incidence of it in the records of the Johns Hopkins Hospital was about 1 in 10,000. Similar figures were given at about that time by Hurwitz at the same hospital and DaCosta at the Jefferson Hospital, Philadelphia. Each year reports have increased the incidence of the disease. According to Dr. Donald Gregg of Wellesley, Mass., Dr. L. B. Morrison, a roentgenologist of Boston, who sees many orthopedic cases, has diagnosed the disease 98 times since the beginning of 1917 in about 15,000 persons in whom the pelvis or long bones were examined by means of the x-ray. This would make a frequency of about one in 150 cases. From all over the world reports of increased frequency of recognition of the disease in its earliest stages have appeared with the universal application of the x-ray to problems of bone disease. Carman of the Mayo Clinic has stated that it is one of the most frequent chronic diseases of the bones. Locke asserts that outside of syphilis it is the most common chronic disease of the bones. The present

paper is based upon 18 cases seen by the writer in the last five years, most of them being referred. There can be no doubt that Paget's Disease is not a rare disease, but a relatively common one and that its recognition is a function of the degree to which the x-ray is applied in the diagnosis of obscure complaints.

THEORIES OF CAUSATION

There is no recognized etiology of Paget's Disease. Some have attempted to maintain that it is a chronic infection of the bones due to some unknown organism, but the evidence for this is so flimsy that it can be immediately discarded. There can be no doubt that Paget's Disease is one of the group of senile or presenile disturbances of metabolism. The question is: What is the nature of this disturbance of metabolism and how can it be controlled? All the evidence points to its being a disturbance of lime metabolism, since the bones are so fundamentally involved. Da Costa, Funk, Bergheim and Hawk, in their very careful study of the metabolism, found a pronounced retention of Ca, P and Mg and a loss of sulphur. The calcium content of the blood is generally within the normal range, although several cases have been described in which it was higher than the normal.* McCrudden, working under the direction of Goldthwaite, Painter and Osgood, found the calcium in the urine high, the magnesium a little low, with a slight loss of phosphorus and a slight retention of calcium and magnesium. These contradictions in the chemical pathology of the disease may be explained as dependent upon the stage in which it is studied, for there are three stages: a stage of decalcification, a stage of new osteoid formation and a stage of inorganic salt deposition in the osteoid. For pathologically, these are the three different stages that may be seen in sections made of the bones. Carman and Carrick have given a good description of how this disease presents roentgenologically. "The whole architecture of the bone is altered, the essential features being porosis and the formation of new bone with hyperostoses, one or the other process predominating in different parts. In later stages the new bone tends to become sclerosed and takes on a dense white appearance with a much decreased permeability to the roentgen rays. The structure of the bone appears to be almost entirely removed and laid down afresh on a different plan and in a different mold. The long bones lose their clear outline, they become curved and the thickening appears to be greatest on the convex surface. In some places subperiosteal thickening is seen, while in others decalcification beneath the periosteum has progressed irregularly."

These changes in the bones produce pathognomonic roentgen-ray pictures. The bones of the skull and the long bones present a moth-eaten or cotton wool appearance of the cortex which is imitated by no other condition. There is also a marked trabeculation, characteristic of decalcification which is absent in Recklinghausen's Disease or osteitis fibrosa cystica

*Koechig, The Calcium Content of the Blood in Pathologic Conditions, J. Lab. & Clin. Med. 9: 679. 1923-1924.

in which the bones look like an unevenly filled sausage, due to the formation of cysts of gelatinous substance accompanied by tumors, reddish brown in color, with abundant giant cells of the myeloma type, and the cortex is reduced to a thin, weak shell. The other disease of the bone from which Paget's Disease has to be distinguished, although it resembles it somewhat, is osteomalacia. Osteomalacia is a pure softening of the bones, accompanied by decalcification and presenting characteristic roentgenograms.

THE RELATION OF ENDOCRINE GLANDS TO BONE METABOLISM

In at least two out of these three related diseases of the bones, osteomalacia and osteitis fibrosa cystica, evidence has accumulated that the disease process is fundamentally an endocrine disturbance. The low calcium content of the blood in osteomalacia, its occurrence under conditions of calcium starvation and excessive calcium loss as in pregnancy, and the occurrence of osteomalacia tetany, all have related it to deficiency of the parathyroid glands in association with other glandular imbalances. On the other hand, much recent work has shown that osteitis fibrosa cystica is a condition of hyperparathyroidism.

The present writer asserted in 1924, when he reported his separation of the internal secretion of the parathyroid glands, that its function is to regulate calcium metabolism by its control of the mobilization of calcium from the stored lime salts of the bones. Studies were soon made of the effect upon the bones of the prolonged administration of it, producing an abnormal mobilization of calcium. It was found, both by direct analysis and by x-ray studies, that the calcium was withdrawn first from the trabecular portions of the long bones, then from the shafts, and last from the cortex. At the same time metastatic calcifications may occur in the thyroid, the lungs, the myocardium, the stomach, duodenum and kidneys.

As early as 1904, Askanazy found a tumor of a parathyroid gland in a case of osteitis fibrosa. In 1925 Hoffheinz, in a survey of the literature, found the relation between parathyroid enlargement and osteitis fibrosa in 17 out of 45 cases of the glandular enlargement. In 1925 Mandel reported a case of osteitis fibrosa improved by removal of an adenoma of a parathyroid. Since then a number of such cases have been reported which have in their ensemble clarified the clinical syndrome of osteopathic hyperparathyroidism, associated with and forming the etiological basis of von Recklinghausen's Disease of the bones, known as osteitis fibrosa cystica. The clinical syndrome consists of pains in the bones, weakness, muscular hypotonia with decreased muscle and nerve excitability, hypercalcemia and hypercalcuria, hypophosphatemia with hyperphosphaturia. Finally, Jaffe, Bodansky and Blair have succeeded in producing the disease in all its characteristics experimentally by the prolonged administration of parathyroid hormone.

All the observations made in the last ten years, physiological and pathological, clinical, as well as laboratory, converge to prove that the in-

ternal secretion of the parathyroid glands is the bone calcium mobilizing hormone. As such, it must function in some catalytic manner; if it does, it becomes possible to conceive that as a regulatory process it must be compensated by some hormone acting in the opposite direction, that is, acting as a *bone calcium demobilizing* hormone, one which assists the bones to take up calcium from the blood, while the parathyroids cause them to liberate calcium into the blood.

In searching for the source of such a hormone the writer was led to the adrenal cortex for the following reasons:

(1) The removal of the adrenal glands is followed by an increased calcium content of the blood.[1]

(2) The injection of extracts of the adrenal cortex which have the power to prolong the life of adrenalectomized animals will lower the calcium content of the blood of normal animals.[2]

(3) The one clinical condition I have observed characterized by a tendency to hypercalcification of the bones is the condition of virilism associated with tumors of the adrenal cortex. I have not seen this reported in the literature of the subject, but in three cases, all in girls between the ages of 14 to 18, I have had under observation, one of the marked items of the roentgenological report has been that concerning the condition of the bones. One, in a girl of eighteen who had a pronounced beard and moustache associated with a general bodily hirsuites with menstrual difficulties, may be quoted as typical. "It is to be noted that the costal arches are completely calcified and there is no evidence of the epiphyses at the crest of the ilia. This child's bony framework corresponds to that of a person of about fifty years of age on account of the premature costal calcification." This hypercalcification could be explained if we assumed that the hyperproduction of the hormone of the adrenal cortex in these cases results in an increased absorption of calcium with the production of a hypocalcemic blood.

These three sets of facts would warrant the view that one of the functions of the hormone of the adrenal cortex is to act as the bone calcium demobilizer, while the parathyroid hormone acts as the bone calcium mobilizer, and the equilibrium between bone calcium and blood calcium can be looked upon as the outcome of a balance between the two. It is interesting in this connection that the complete removal of either one of these glands results in the production, in the space of 48 hours, of a frequently fatal acute intoxication, due to an interference with the normal processes of metabolism, and the production in undue amount of poisonous metabolites.

Now the pathology of Paget's Disease has been described as follows by Packard, Steele and Kirkbride. There is:

(1) Absorption of the compact substance, causing enlargement and confluence of the Haversian canals.

1. Personal observations and also Rogoff and Stewart, Am. J. Physiol. 86: 20. 1928.
2. Personal observations and Mervish and Bosman, Brit. J. Exper. Biol. 6: 350. 1929.

(2) Formation of new bone which runs diffusely through the affected and adjacent healthy portions. This new bone remains uncalcified and is in turn reabsorbed.

(3) The conversion of the medullary substance into a vascular connective tissue containing fat cells, giant cells and leukocytes. In a small proportion of cases, cysts filled with gelatinous material and giant celled sarcomas occur in the medulla.

(4) As a consequence of these three processes the ordinary relations of the compact substance and medulla are destroyed. The bones become greatly thickened and asymmetrical, but since the new bone remains uncalcified, the elasticity permits of great deformity of the long bones from weight of the body.

Prince divides the pathology of Paget's Disease into three stages:

(1) Absorption of bone, (2) new formation of bone without calcification, and (3) new formation of bone with calcification. The x-ray picture may show all three of these processes.

In view of these considerations, the following conception of Paget's Disease presented itself as consistent with the evidence from the pathological anatomy and the pathological biochemistry of the disease.

(1) The first or absorptive decalcifying stage of the disease is due to a hyperfunctioning of the parathyroid glands in relation to a relative deficiency of the interrenal gland (adrenal cortex). During this stage, the bones soften and deformities occur.

(2) The second or hypercalcifying stage of the disease is due to an excessive compensation of the interrenal glands (adrenal cortex) with a relative deficiency of the parathyroids.

(3) Various intermediary stages represent different degrees of imbalance between the parathyroids and the adrenal glands.

In the treatment of the first stage, the stage at which most of the most acute symptoms are present and the deformity begins to develop, the logical procedure would be to use the hormone of the adrenal cortex, and also a high Vitamin C diet. The high Vitamin C diet was used because there is evidence of a defective calcification of bones in scurvy and also that the normal integrity of the adrenal cortex depends upon a sufficiently high supply of Vitamin C. My attention was attracted to this by the statement of McCarrison that: "I have been much impressed by finding that the histo-pathological changes I have described (changes of degeneration) were present in the adrenals of guinea pigs, fed on the scorbutic dietary, which exhibited during life no clinical evidences of scurvy. Depression of adrenal function may therefore be regarded as a prescorbutic manifestation of a dietary deficient in accessory food factors of the "C" class. A scorbutic diet causes pronounced depreciation in functional capacity of the adrenal glands.

An extract of the cortex of the adrenal glands, standarized by its capacity to lower the calcium content of the blood was used.

Fresh adrenal glands were obtained from the slaughter house as soon as possible. Later it was found that glands which had been frozen for a few hours could also be used. The fat was trimmed off the gland with a scissors and the gland was halved, exposing the medulla, which was carefully cut out, going a little beyond the line of demarcation between the cortex and the medulla. The glands were then put in a meat grinder and ground. They were then put in double their volume of 95 per cent ethyl alcohol and allowed to stand for 24 hours. They were treated thus with alcohol three times. All the alcohol extracts were combined and the alcohol was evaporated. The residue was then taken up in ether and filtered. To the filtrate was added an equal quantity of acetone to precipitate the phosphatids. This was filtered again and the filtrate then evaporated. The residue was dissolved in a small quantity of alcohol, placed in an ice-box over night. This was followed by crystallization of the content of cholesterols. These were filtered off, the alcohol evaporated, the residue was dissolved in ether and filtered. The ether was evaporated, yielding a small quantity of the yellowish oil which was shown to be or contain an active principle of the adrenal cortex. For use, it was dissolved in 95 per cent alcohol containing 2 per cent hydrochloric acid by volume. The alcohol was then distilled off in vacuo, the remaining fluid neutralized with sodium hydroxide, then diluted with water to make the concentration of sodium chloride 0.9 per cent. This was then passed through Berkfeld filters and tested for sterility by the standardized methods before being put up for injection.

This was the first method used. In a subsequent method, the glands were extracted directly with ether several times, actone was added to the filtrate, the phosphatids filtered, ether evaporated, the residue dissolved in a small quantity of alcohol to allow for crystallization of cholesterol in the cold; after filtration and evaporation of the alcohol, the residue was redissolved in ether and evaporation of the ether yielded the same kind of yellowish oil which was treated as above to be prepared for purposes of injection.

Several kilograms of the adrenal glands were used each time. This extract produced satisfactory results in 16 cases out of 18 cases treated in the last six years. It was effective even when no special attention was paid to the diet. But the high Vitamin C diet was found helpful as an adjuvant, assisting the unproved functioning of the adrenal cortex.

Case I. I began treating my first case in 1925 with an extract of the adrenal cortex, the effect of which, upon the calcium content of the blood of normal animals, I was studying at the time. This patient was a woman 49 years of age who had passed the menopause at the age of 44. For two years she had had practically constant pain deep in the legs, the hips, elbows and fingers. At the same time her hips, knees and ankles had become stiff. Her head had enlarged. She presented the typical facies of Paget's Disease. The tibiae were markedly irregular and roughened. Roentgen examination of the skull showed the typical appearance of Paget's Disease, and the greater tuberosities of the tibiae showed particularly well marked changes. She was put on a high calcium, high Vitamin

C diet and was given hypodermic injections of a blood calcium-affecting adrenal cortex extract prepared by a process involving the use of lipin solvents with final solution in an aqueous medium. These were given three times a week for six months. At the end of that time there were no pains, and the stiffness of the knees, hips, and ankles was no longer present. X-ray examination showed no further progress of the Faget's with some slight tendency to greater calcification of the affected areas. The patient has been under observation every six months since, and the disease has apparently been arrested.

Case II was that of a woman 52 years of age. The illness began four years before with pains in the head, eyes and legs. There was a sudden loss of voice which occurred several times in the space of a few months. She was advised to have her tonsils removed and this was done. Her arthritic trouble began after the removal of the tonsils with marked pains in the legs. Arches were made. Her knees bothered her very much and both knees were put in a plaster of Paris cast. The legs became bowed after the removal of the casts. The head pains continued and the patient perspired a great deal. There was a total lack of vitality. The basal metabolic determination was —21 per cent, blood calcium 11.8, phosphate 3.2. X-ray examination of the skull showed typical Paget's Disease. She was put on a high calcium, high Vitamin C diet with hypodermic injections of adrenal cortex hormone for about a year. At the end of that time, there was no more pain in the head or legs, there was no further increase of the deformity and there was a marked increase of vitality accompanying a change in the basal metabolic rate to 4 per cent. This woman has been seen at regular intervals since and there have been no subjective complaints, no increased bowing of the legs and no further appearance of the disease process anywhere else in the body.

Case III was that a man 58 years of age. The chief complaint was attacks of paroxysmal fibrillation of the heart, not relieved by digitalis nor quinidine. For about 20 years he had had rheumatic pains in the lower extremities which seemed to be worse after exercise. For about one year there had been stiffness and marked pain in the left knee. The voice tended to become weak, so that it was almost impossible for him to speak. There had been increasing impairment of the hearing for about a year. The basal metabolism determination was—18 per cent, uric acid 4.8, calcium 11.5, phosphate 3.9, cholesterol 192. The urine showed sugar and many calcium oxalate crystals. X-rays examination showed the typical picture of Paget's Disease in the skull, spinal column, tibiae and pelvis. He was put on a high calcium, low phosphate diet with hypodermic injections of adrenal cortex hormone. During the first month there were several attacks of paroxysmal fibrillation of the heart. After that they became much more infrequent, as much as two or three months apart with a final cessation of attacks, although extra systoles were noted from time to time. The pains in the extremities and the limitation of movement in the left knee was relieved. The general health improved greatly, with a return of vitality and strength. There was improvement in the voice and hearing which made it possible for him to return to work. No deformity developed.

Case IV was that of a man 48 years old. The chief complaint was pains in the legs. About three years before he began having a dull aching pain in the left tibia at night which was relieved by massage with oil. Then a steady pain developed in both legs. The head had enlarged gradually for about five years. Physical examination showed some anterior bowing of both tibiae with roughening of the edges. The basal metabolic determination was 20. Blood chemistry showed sugar 82, uric acid 4.4, cholesterol 190, calcium 10.8 and phosphate 4.5. The urine showed sugar and many calcium oxalate crystals. X-ray examination of the skull showed a typical Paget's Disease picture. The patient was put on a high calcium, high Vitamin C diet, and the adrenal cortex hormone was given hypodermically three times a week. There was complete relief of pains in the legs and in the ribs. No further increase in deformity of the tibiae occurred after four years. There was a marked restoration of general health and strength and a return to economic activity. I may mention that before being seen he had been given parathyroid extract and was made much worse by it. I may also mention that all of the above described patients said their pains were increased and they felt generally worse whenever parathyroid hormone was given to them hypodermically. The features of the series of 18 cases I have treated with a high calcium diet and hypodermic administration of a hormone of the adrenal cortex are presented in the chart.

	Chief Complaint	Duration	X-Ray Diagnosis	Result of Treatment With Adrenal Cortex
A. R.	Constant deep pain in legs, hips, elbows and fingers.	2 years	Enlarged skull Paget's Disease	Complete relief of pain, no development of deformity after six years, no further enlargement of head.
J. B.	Pains in the head, eyes and legs.	4 years	Enlarged skull Paget's Disease	Complete relief of pains in head, eyes and legs, no deformity after 4 years.
J. A.	Attacks of fibrillation of heart, stiffness and pain in left knee.	1 year	Enlarged skull Paget's Disease	Only occasional extra systoles, no pain or stiffness in joints, no deformity after 4 years.
R. S.	Pains in legs, especially in shin bones.	3 years	Enlarged skull Paget's Disease	Treatment discontinued too soon to record results.
A. D.	Rheumatoid pains in knees, ankles and hips.	2 years	Enlarged skull Paget's Disease	No pain, no deformity after 5 years.
E. R.	Headaches.	1 year	Enlarged skull Paget's Disease	No headaches, no deformity after 5 years.
B. A.	Pains in legs, slight bowing.	3 years	Enlarged skull Paget's Disease	No pain, no further deformity.
E. Y.	Stiffness and soreness of joints, knees particularly.	2 years	Enlarged skull Paget's Disease	No stiffness, no soreness, no deformity after 3 years.
O. W.	Weakness and palpitation.	1 year	Enlarged skull Paget's Disease	Relief of heart symptoms, return of strength.
G. B.	Pain in thighs; weakness.	3 years	Enlarged skull Paget's Disease	Marked increase of strength; freedom from pain, no deformity.
H. R.	Pains in back and head, noises in ears.	2 years	Enlarged skull Paget's Disease	Relief of pain; no more noises in ears.
J. M.	Pains in shin bones, legs and back.	3 years	Enlarged skull Paget's Disease	Pains almost entirely gone; return to activity; no deformity.
R. E.	Pains in knees, attacks of lumbago.	4 years	Enlarged skull Paget's Disease	No more attacks of lumbago; freedom from pain and deformity.
N. S.	Stiffness in legs, pain in back.	1 year	Enlarged skull Paget's Disease	Treatment discontinued too soon to record results.
R. K.	Headache, pain in back and thighs; legs becoming misshapen.	5 years	Enlarged skull Paget's Disease	Relief of pain and headache, no further deformity.
S. B.	Attacks of palpitation, change in size of head.	4 years	Enlarged skull Paget's Disease	No more heart symptoms; no increase in size of head or deformity.
D. F.	Pain and stiffness in knees; pains in chest.	3 years	Paget's Disease Enlarged skull	
P. M.	Deafness, buzzing in ears.	6 years	Enlarged skull Paget's Disease	Hearing improved; no more buzzing in ears.

SUMMARY

1. Paget's Disease is an entity representing a disturbance of bone metabolism involving an imbalance between the parathyroid glands and the adrenal glands, there being excessive function of the former and deficient function of the latter.

2. In 16 out of 18 cases, the regular administration of adrenal cortex hormone with a high calcium diet produced a relief of the pains in the extremities and the head, a restoration of the sense of health and well-being with a return to occupational activity, and an apparent arrest of the disease as shown by the cessation of development of deformity and the symptoms of sympathetic nervous system irritability. The course of

Paget's Disease is chronically protracted; in general, its progress is downward. The results of the cases reported, although they are limited in number, and have still to be checked and watched, justify the conclusion that adrenal cortex hormone is a valuable remedy for a disease which has hitherto had no remedy at all.

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HYPERPITUITARISM BEGINNING IN INFANCY

THE ALTON GIANT

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Giants over seven feet tall are extremely uncommon. Usually if not always they exhibit disturbed function of the pituitary gland as an etiological factor in their abnormal development. The pathological condition is ordinarily associated with delayed closure of the epiphyses. According to Biedl (1) the abnormality most often begins at puberty and may continue far beyond the normal period of growth even to the age of 25 or 30. Cases of earlier gigantism are excessively rare and have not been thoroughly studied during the period of childhood and adolescence. It is of interest, therefore, that during the past 18 months we have had the opportunity of observing intimately a boy who at the time of his first admission was eleven years old but who had grown abnormally and continuously from the age of six months.

R. W. of Alton, Illinois, was first seen at Barnes Hospital on January 25, 1930, when he was 11 years and 11 months of age. He was not ill and came because his father was interested in having him examined.

Family History: In three generations there have been no extremely large people on either side of his family. His maternal grandmother is fat but not tall. His father is a slender man about 5 feet 11 inches in height. His mother is of medium height and weights 140 pounds. He has two sisters and one brother of normal size.

Past History: At birth he weighed only nine pounds but began almost immediately to grow at an abnormal rate. At six months he weighed 30 pounds. During the first year he developed a rupture which remained unrepaired for several months. He started to walk at the age of 12 months. At a year and a half, he weighed 62 pounds and by the time he was two years old his extraordinary size attracted general attention. At six he entered school in a suit which was the largest his father could buy for a boy and which was labeled size 17. When he was nine, he measured six feet one inch, weighed 178 pounds and was able to pick his father up and carry him about.

There was no history of injuries. He had measles in early childhood and whooping cough in the autumn of 1929.

He suffered from headaches whenever he read or studied. Examination of his eyes showed a moderate myopia but the headaches disappeared when he wore his glasses. He had always drunk large quantities of water and had to get up occasionally at night to urinate. This never was, however, a prominent symptom and did not seem to indicate any degree of diabetes insipidus. His appetite was vigorous. He had always eaten more than other members of the family but had attracted no great attention because of extraordinary gastronomic feats.

His record in school had been excellent and he was the youngest boy in the second half of the seventh grade in the public school at Alton.

Examination at the time of the first visit was accomplished with considerable difficulty. The boy was so shy as to appear depressed and almost stupid. He was extremely modest and would allow only partial exposure of his body. He became sulky and finally wept when x-ray pictures were suggested. His interest, however, was easily excited and sustained. He was greatly diverted by a pocket flashlight which one of the doctors carried and he displayed genuine amusement when he was encouraged to perform feats of strength. While in the

photographic studio he picked up without any apparent effort the somewhat astonished photographer who weighed over 150 pounds.

His expression and appearance are best shown by the photographs. Notable is the wide spacing between the eyes and the complete absence of mandibular prognathism. There was some spreading of the upper teeth. The skin was moist, delicate and of fine texture, but the hands and feet tended to be cold and slightly cyanotic. He had no hair on his face and the hair on his body was scant. His father reported that he had a small amount of pubic hair and the genitalia might be considered small for an eleven-year-old boy. His pupils were

Fig. 1. Front view and profile of patient at the age of 11, showing somewhat characteristic facies of preadolescent hyperpituitarism and complete absence of mandibular prognathism.

equal, regular and reacted to light and accommodation. The visual fields appear in Figure 2. Except for a small central scotoma in the right field and enlarged blind spots on both sides, they displayed no abnormality. The apparent con-

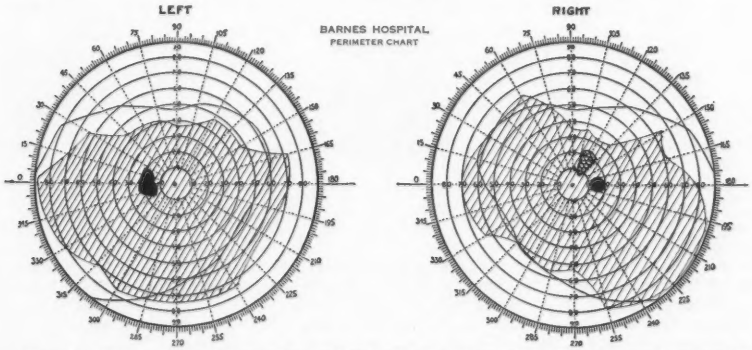

Fig. 2. Visual fields taken when patient was 11 years old. The apparent contraction of the upper and temporal fields is attibutable to a slight drooping of the lids. The enlarged blind spots and the small right central scotoma are apparent.

traction of temporal and upper fields was attributed to a slight drooping of the lids. His visual acuity was 10/100 on the left and 10/50 on the right.

Examination of the heart, lungs and abdomen revealed no abnormalities. Deep reflexes were present and active. Both hands and feet were beautifully shaped in spite of their enormous size.

Measurements

Weight	112.3	kgm.
Height in bare feet	208.0	cm.
Sitting height	103.5	"
Arm spread	203.5	"
Circumference of head Fronto—occipital	65.5	"
Circumference of chest at nipples	104.5	"
Circumference at umbilicus	94.0	"
Circumference at iliac crest	92.0	"
Circumference at trochanters	110.5	"
Length of clavicle	19.0	"
Acromion to tip of third finger	91.0	"
Length of hand—proximal end of third metacarpal to tip of third finger	22.0	"
Length of third finger	14.5	"
Length of foot	37.0	"

The x-ray examination revealed in the bones of the face and maxilla a moderate tendency to prognathic development. The mastoids showed extraordinary development of pneumatic structure, the cellular elements extending into the squamous portion of the temporal bone and partially obscuring the outlines of the sella turcica. The sella was of extreme size measuring 2.5 cm. in its antero-posterior diameter. The floor of the sella showed a loss of continuity being broken by a tubular structure which extended downward and forward from the sella and reached almost to the posterior wall of the pharynx where there was an indefinite soft tissue shadow encroaching upon the lumen of the pharynx itself.

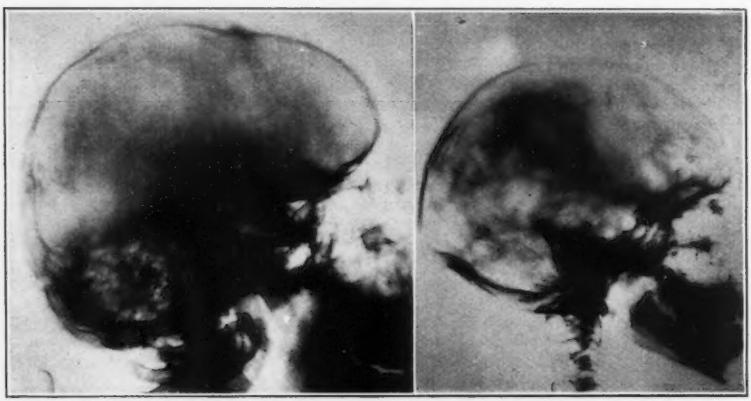

Fig. 3. Skull of patient at the age of 11, compared with that of normal boy of the same age. Noteworthy is the extraordinary development of the mastoid air cells. The sella which measured 2.5 cm. in its anteroposterior has been outlined with dots to indicate its extent.

Dr. Sherwood Moore who saw these plates thought that in addition to the highly abnormal sella turcica there was evidence of a persistent Rathke's pouch. In Figure 3 the skull may be compared with the skull of a normal sized boy of eleven.

A similar comparison may be made of the hands which, although of extreme size, were symmetrical as to their integral parts. The epiphyses in the two eleven-year-old boys seem to have reached an almost indentical stage of

development. The somewhat tapering fingers of the patient are shown to better advantage in Figure 5 where they appear beside the hand of a man 6 feet in height.

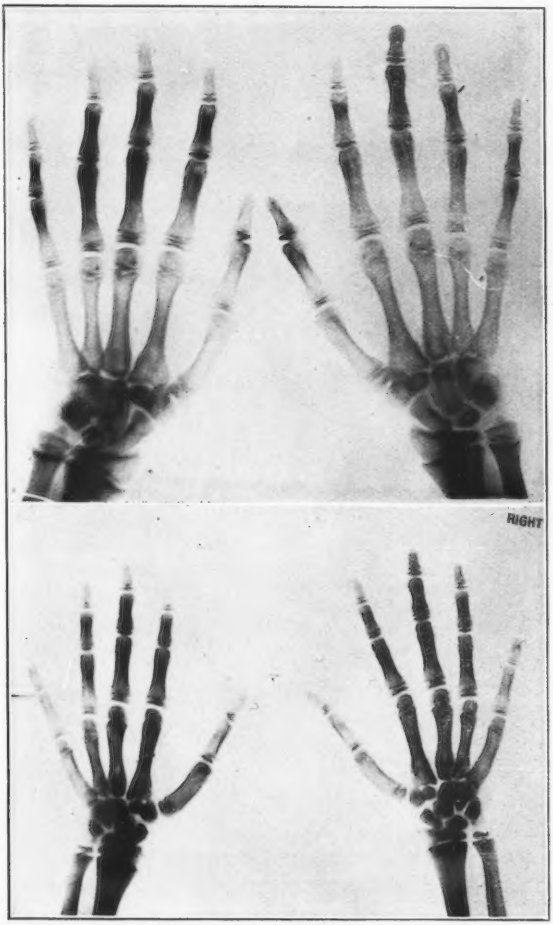

Fig. 4. X-ray photograph of hands of patient at the age of 11, compared with those of normal boy of same age. There was no considerable difference either in the state of the epiphyses or in the degree of calcification.

The patient was examined again in February, 1931, one year and a month after the first examination and at almost exactly the time of his thirteenth birthday. He had had a good year. At school he was in the 8th grade and ranked in the upper middle of his class without studying at home. He had lost much of his bashfulness and was interested and co-operative in all of the tests. His physical strength had not declined. He made a formidable center on the local basketball team. Several days before he came to the hospital he had been on a thirteen-mile hike without excessive fatigue. The physical development of the year seemed satisfactory for his age. The external genitalia had increased slightly in size. There was a greater growth of pubic hair but no history of erections.

Fig. 5. Hand of patient compared with that of a man six feet in height. Noteworthy are the long, slightly tapering fingers and the delicate, fine skin.

Measurements

Weight	126.4	kgm.
Height in bare feet	219.0	cm.
Arm spread	215.0	"
Circumference of chest at nipples	107.5	"
With full expansion	113.0	"
Circumference at umbilicus	104.0	"
Circumference at iliac crest	105.0	"
Circumference at trochanters	116.0	"
Length of clavicle	19.0	"
Acromion to tip of 3rd finger	97.0	"
Length of hand—proximal end of 3rd metacarpal to tip of 3rd finger	23.5	"
Length of 3rd finger	15.5	"
Length of foot	38.5	"

X-ray examination of the skull showed a progression in the growth of all bones with continued overgrowth of the pneumatized structures.

Examination of the eyes by Dr. H. N. Fisher showed a compound myopic astigmatism with visual acuity of 6/30 in both eyes. Aside from slight myopic changes, the fundi appeared normal. The visual fields corresponded to those obtained the year before except that the small scotoma in the right field was no longer apparent.

The boy's appearance in July, 1931, at the age of 13 years and 6 months is shown in Fig. 6 where he stands with his nine-year-old brother and his father whose height is five feet eleven inches.

At this visit, he measured 221.5 cm. in height. He was wearing a 7⅞ size hat which had been specially made to order. Gloves were shaped from a diagram of his hands. His shoes were estimated to be size 30 and measured 43.3 cm. in length and 13.3 cm. in width. During the past few years each last

of his shoes, which were made to special order had supplied him with about two pairs before it was necessary to increase the size for the growth of his feet.

Examination of the genitalia showed moderate hair growth in the pubic region without evidence of hair between symphysis and umbilicus. The penis was small, about 10.0 cm. with a long prepuce. The testicles were small. There was no hair in the axillae, no beard and only a slight amount of hair on the thighs.

At this time, various tests were performed. His oral temperature was 36° C, red blood cell count was 4,830,000; hemoglobin was 95 per cent, white blood cells numbered 6,900 with a normal differential count. The Kahn reaction was negative. The urine examination revealed no abnormalities.

A sugar tolerance test was incomplete because of the objections of the patient to the withdrawal of blood. The fasting blood sugar was 110 mgm. One hour after the ingestion of 240 gm. of glucose the blood sugar was 142 mgm. No sugar appeared in the urine for one and a half hours following the ingestion of the sugar.

The oxygen consumption was considerably below normal.

Fig. 6. The patient at the age of 13 is shown with his brother, who is 9, and his father.

DISCUSSION

This patient began to grow at an abnormal rate almost immediately after birth. He was already unusually large at the age of six months. His father states that from that time his growth was continuous without spurts or notable periods of quiescence. Such a history appears to be almost unique. As a somewhat similar instance may be mentioned the Portuguese giant reported by Magalhaes Lemos (2). This man was 21 years old and was said to have been larger than normal at birth. His extraordinary growth started, however, at 6 or 7 years, following an at-

tack of smallpox. From this time it continued steadily until the age of 12. When first seen he was 21 years old and measured 210 cm. in height. In this connection one should also mention the Bulgarian giant described by Falta (3) who began to grow at the age of 7 and who measured 206 cm. at the age of 12.

Sutton (4) has collected the histories of a small number of patients who had been considered giants during childhood. Her own patient was a thin girl measuring 162.5 cm. and wearing size 9 shoes at the age of 11. The sella turcica was not enlarged but showed a bridging across the upper portion of the fossa. Leri and Seconte (5) described a child of 6 who had attained the height of 136 cm. and the symmetrical development of a girl of 12. Kundratitz (6) told of a boy of 10 whose height was 142 cm. Compared with our patient, the gigantism of these cases is not impressive. More significant is the patient of Brissaud and Meige (7) who started to grow rapidly at 7 years and who at 21 had attained a height of 210 cm. and an arm span of 240 cm.

Not to be confused with the pituitary giants are the patients with overgrowth and sexual precocity probably dependent upon lesions of the pineal gland. Such cases have been reported by Fein (8) and by McNeil (9).

The height of our patient has been exceeded by a number of the famous giants. The skeleton of O'Byrne, which is supposed to have cost John Hunter £500, measured 249 cm. Cushing's (10) giant, Turner, was 251.5 cm. tall and the skeleton of the Irish giant at Trinity College measures 259 cm. There are several authentic records of men and a few women who were more than 220 cm. in height. For the age of 13, however, the height of 221.5 cm. is extraordinary and the present rate of growth, 13.5 cm. during the last year and a half, indicates that this boy may attain a size rivalling the largest of the giants. The possibility seems greater when it is remembered that the most rapid growth of Cushing's giant occurred after the age of 15 and that many subjects of hyperpituitarism have continued to grow after they were 20 years old.

Of interest in this regard is the size of the feet and hands. It has often been noted that in pituitary gigantism the growth is at first most marked in the extremities and particularly in the feet. It may be indicative of the potential growth of our patient that at the age of 13 his feet measure 38.5, 0.5 cm. longer than the shoe of Cushing's patient, whose height was 32.5 cm. greater! His hands from the base of the third metacarpal to the tip of the third finger measured 23.5 compared with 27.0 cm. in Cushing's giant.

Relatively narrow shoulders have been seen in many of the larger giants. It is therefore significant that in a year of rapid growth during which there was an increase in height of 11.0 cm., in arm spread of 11.5 cm. and in the circumference of the iliac crest of 13.0 cm., the length of the clavicles remained entirely stationary.

The size of the pituitary fossa which in its anteroposterior diameter measured 2.5 cm., may be compared with the sella in Cushing's patient, the dimensions of which were 2.7 by 1.7 cm. The huge development of the pneumatized cavities of the skull in giants has been noted by several observers. Cushing reported enormous maxillary and frontal sinuses in Turner's skull. In our patient, the development of the mastoid cells is almost without parallel. The x-ray shows also unusual pneumatization of the squamous portion of the temporal bones.

Except for the enormous size of the sella turcica, local signs of pituitary involvement are almost entirely absent. The headache of which the patient has complained is apparently due to a myopia and is easily corrected by proper glasses. There has been no strabismus nor paralyses of cranial nerves. The eyegrounds and visual fields fail to indicate any increase in intracranial pressure. The polyuria is not sufficiently marked to indicate diabetes insipidus. The association of a huge sella with the continued abnormal growth of the bony skeleton is sufficient evidence to establish the diagnosis of active hyperpituitarism. The other signs which might indicate dysfunction of the pituitary are somewhat equivocal and, as is usual in these cases, are difficult to interpret.

Although irregular breathing prevented exact determination, the basal metabolic rate is below normal and may be very low. This observation, coupled with the cold hands and feet and the tendency to subnormal temperature, might be interpreted as evidence of hypothyroidism. The delicate skin and abundant hair of the head, the alert intelligence raise a doubt as to the correctness of this explanation and suggest that the low basal metabolism may depend on other and possibly on pituitary factors. The sugar tolerance test, although incomplete, may indicate an increased tolerance for carbohydrates.

It is extremely difficult to judge whether there is in this patient any retardation of sexual development. The penis and testicles seem extremely small when compared with the enormous size of the patient. Variability in the size of genitalia at this age is so great, however, as to make conclusions impossible. The hair growth, though scant, is not abnormal for a boy of 13. The father has noted during the past year many psychological evidences of increasing sex consciousness.

SUMMARY

A case of preadolescent gigantism of pituitary origin has been reported. An extraordinary feature is the beginning of abnormal development in early infancy. Growth has been steady without spurts during the entire period of childhood and has continued at an undiminished rate during 19 months of observation. Of special interest is the low basal metabolic rate accompanied by subnormal temperature and cold hands and feet. Remarkable, also, is the extraordinary size of the mastoid cells and the pneumatization of the squamous portion of the temporal bone.

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THE SPECIFICITY IN THE ACTION OF THE ANTERIOR PITUITARY OF DIFFERENT MAMMALS AS WELL AS OF URINE OF PREGNANT WOMEN ON THE SEX ORGANS AND THYROID GLANDS OF IMMATURE FEMALE GUINEA PIGS*

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In previous investigations Loeb and Bassett (1) have found that it is possible to produce through a small number of injections of acid or alkaline extracts of anterior pituitary of cattle into guinea pigs in the thyroid gland of this species a state of hypertrophy corresponding to the condition observed in very pronounced cases of Graves' disease in man. In view of the relations which have been established between the anterior pituitary and the function of the sex organs (2), it was of interest to correlate the effects of anterior pituitary on the thyroid with those exerted by this gland on the sex organs. For this purpose we began about two years ago a comparative study of the action of the anterior pituitary of various mammalian species on ovary, vagina, uterus, mammary gland and on thyroid gland; in the beginning of the winter, 1930-31, we included in these investigations also the effect of urine of pregnant women on the thyroid and sex organs. We have already referred to some preliminary results obtained in a previous communication (3). We stated there that the effects on the thyroid gland and those on the sex organs do not parallel each other; in this case we used as criteria for the activity of anterior pituitary preparation on the sex organs, ovulation, hypertrophy of the uterus and opening of the vagina in the guinea pig. On the other hand, we found a correlation between production of interstitial gland and pseudocorpora lutea in the ovary and hypertrophy of the thyroid gland. Since then we have continued our investigations, and we shall here give a complete summary of the results obtained.

We used in these experiments in the large majority of cases guinea pigs varying in weight between 170 and 200 grams. In some cases we used still younger guinea pigs, and in a small number of experiments older guinea pigs during various stages of the sexual cycle. Pieces of anterior pituitary of cattle, as well as pieces of the residue remaining after acid extraction, pieces of guinea pig, rabbit and cat anterior pituitary were inoculated subcutaneously, while acid and alkali extracts of cattle anterior pituitary as well as urine of pregnant women were injected as a rule intraperitoneally. It may be stated that the number of experiments on which our conclusions are based is very great and that at the conclusion of each

*These investigations were carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

experiment both ovaries were cut into serial sections, while in case of the vagina, cervix, mammary gland and thyroid parts of the organs were studied microscopically.

I. INOCULATION OF ANTERIOR PITUITARY OF GUINEA PIG

The anterior pituitary glands of adult male guinea pigs varying in weight approximately between 350 and 500 grams were used for inoculation into immature female guinea pigs weighing generally between 170 and 200 grams. The number of successive daily inoculations varied in different experiments between 3 and 10. The number of anterior pituitary glands inoculated daily varied in individual experiments between 1 and 4; in this way we tried to eliminate as much as possible the effects of differences in the quantity of material inoculated. Thirty experiments were made altogether and in seven of these four anterior pituitary glands were inoculated daily. The latter experiment alone required for inoculation the anterior pituitary glands of more than 120 guinea pigs; in every case the glands were taken out directly after the death of the animal.

The effects of anterior pituitary of guinea pig came out most clearly in those experiments in which four glands were inoculated daily; but in principle the effects are the same after inoculation of less material, although the results are here somewhat less pronounced and perhaps not quite so regular. After daily inoculation of four glands over periods of four or five days the effects are as follows: The growth of the follicles is stimulated; a considerable number of very large, very mature follicles develops. The granulosa of these follicles undergoes the typical changes of maturation; the eggs may begin to undergo maturation and the first stages of an abnormal segmentation before any degeneration of the granulosa has taken place. Then typical ovulation may occur with expulsion of the egg from the open follicle and with subsequent formation of corpora lutea. After these have begun to form, a second ovulation may occur soon after the first. At the same time we may see in such cases structures resembling typical small young corpora lutea except that eggs are retained, surrounded either by the central connective tissue or by lutein tissue. These structures represent either follicles which ruptured during ovulation, but in which the eggs were retained, or they are mature follicles, in which blood vessels and connective tissue grew into the granulosa, some time after full maturation had been reached. We may also find large follicles in early stages of connective tissue atresia. However characteristic is the tendency on the part of the not yet fully developed follicles to continue to grow, instead of undergoing premature atresia as happens in the case of so many follicles in the normal guinea pig ovary. Evidently the growth stimulus acting on the ovarian follicles counteracts to some extent, although not completely, the tendency to degenarative processes in growing follicles. Even the tendency of all large, but not yet mature follicles and of medium sized follicles to undergo atresia at the time just preceding

ovulation, was partly, but not entirely counteracted by the effect of the growth stimuli.

The theca interna does not as a rule show any noticeable enlargement, but behaves about in the normal manner. So-called interstitial gland is not usually produced, except that some small strands of such tissue may be found occasionally around the vessels of the medulla; the theca interna does not enlarge and does not usually participate in the formation of interstitial gland; if hypertrophy takes place here, it is an exceptional occurrence. In one case, in which the glands before inoculation had been kept in a frozen state from one to several days, all the large follicles had been converted into pseudolutein bodies, with retained eggs, presumably as a result of the maturation of many large follicles with subsequent ingrowth of vessels and connective tissue. Partial proliferation of the vagina in this case indicated that probably maturation of follicles had preceded this process of formation of pseudolutein tissue. The medium sized follicles had undergone atresia. Presumably a rudimentary ovulation had taken place in this case leading to this condition. In another experiment, in which the anterior pituitary glands had likewise been frozen before inoculation, the effect did not vary from that obtained by inoculation with normal glands. Accompanying these changes in the ovaries, proliferation in the epithelium of the vagina, which normally accompanies the presence of mature follicles and precedes ovulation, occurs. But it is remarkable that in the majority of cases this proliferation and conversion of the typical vaginal epithelium into squamous epithelium remains incomplete. The stage of perfect keratinization is not usually reached; but it seems that it may occur, in cases in which ovulation from mature follicles, not complicated by other changes had taken place in the ovary. The uterus usually shows a very high surface epithelium without mitotic proliferation in the glands and without predecidual changes in the mucosa after inoculation of four anterior pituitary glands; this structure corresponds to the oestral condition of the uterine mucosa. In the typical cases here described the mammary gland is actively proliferating.

On the other hand, the thyroid gland in these experiments with daily inoculation of four anterior pituitaries, does not show any hypertrophic change, nor is there any indication that the liquefaction and absorption of the colloid were accelerated in any noticeable way by this procedure. As we have stated previously, anterior pituitary of cattle has a very pronounced hypertrophying effect on the thyroid gland of the guinea pig. Usually the cattle gland had been kept on ice for some time before inoculation. We could, however, show that this factor is not responsible for the difference in the behavior of cattle and guina pig gland; if we kept the latter on ice in the same way as we did in the case of the cattle gland, the ineffectiveness of the guinea pig anterior pituitary was not thereby altered in the least. However, in other experiments, with inoculation of smaller quantities of guinea pig anterior pituitary, in some cases a very slight

stimulating effect on the thyroid gland was observed, but in every case it was very slight and very much less than observed after administration of cattle gland.

However, when we combined daily intraperitoneal injections of acid extract of cattle anterior pituitary with inoculation of anterior pituitary of guinea pig the thyroid gland showed the typical hypertrophic changes; while the sex organs showed essentially a condition characteristic of acid extract of anterior pituitary of cattle, namely, a tendency to the formation of hypotypical follicles, with or without the formation of small theca interna lutein bodies and interstitial gland, combined with a resting state of the vagina. The uterus usually showed some stimulation of the connective tissue of the mucosa as well as of the uterine glands. This was perhaps due to a stimulating effect exerted by the pseudolutein tissue; it is possible that the latter has certain functions in common with the real corpus luteum.

We may then conclude that on the whole a complete or relative lack of effect on the thyroid gland, and a tendency to cause maturation of the follicles with subsequent ovulation, accompanied by the formation of granulosa, pseudolutein bodies, and the absence of a pronounced tendency to cause the transformation of theca interna into interstitial gland are characteristic of the action of anterior pituitary of the guinea pig.

II. INOCULATION OF ANTERIOR PITUITARY OF RABBIT

In different experiments the quantity of anterior pituitary inoculated daily varied between two glands and one-half of a gland of male rabbits varying in weight approximately between 1400 and 2000 grams. Successive daily inoculations during periods varying between two and eleven days were made. The effects of administration of anterior pituitary of rabbit resemble those of administration of guinea pig gland in so far as both accelerate growth and maturation of follicles; in this case also the action of the growth promoting factor counteracts to some extent those conditions which lead to a degeneration of granulosa in many follicles that have not yet grown to full size and matured. Inoculation of rabbit anterior pituitary also counteracts to some extent, but not altogether, the effect of undernourishment, which latter effect consists in the production of hypotypical follicles with the corresponding changes in the other sex organs. Rabbit anterior pituitary not only accelerates the growth of follicles and the maturation of follicles which have reached full size, but it may also induce in some cases premature maturation of the granulosa of small or medium-sized follicles, thus inhibiting their further growth. However, inoculation of the rabbit anterior pituitary also causes the conversion of large mature follicles into granulosa pseudolutein bodies by inducing the ingrowth of capillaries and connective tissue from the theca interna into the granulosa. Moreover it is responsible for the transformation of not yet fully grown, retrogressing follicles, during the stage of connective tissue atresia,

into theca interna pseudolutein bodies with their characteristic hypertrophy of theca interna; furthermore it induces a similar hypertrophy of the theca interna in follicles which are in the last stage of connective tissue atresia; this latter process leads to the production of the so-called interstitial gland. Cell strands surrounding the vessels of the medulla of the ovary also participate in the formation of interstitial gland. It seems that in the pseudolutein bodies at later stages the hypertrophic theca interna alone remains prominent and thus in the end these structures may appear more or less as parts of the interstitial gland. Therefore, the effects of rabbit anterior pituitary gland differ from those of guinea pig anterior pituitary in that the former, in addition to promoting the growth of follicles, calls forth to a much larger extent than the latter the various types of luteinization. Furthermore, while the guinea pig anterior pituitary induces ovulation, no ovulation was ever observed by us after inoculation of rabbit anterior pituitary. It is possible that the more prominent role which the interstitial gland and the pseudolutein bodies play in the latter case, prevents ovulation. It is of interest to consider in this connection the fact that also in the normal rabbit ovary the interstitial gland is much more prominent than in the guinea pig ovary and that while in the latter a spontaneous cyclic ovulation occurs, it does not occur in the rabbit. Is the difference in the activity of the anterior pituitary glands in these two species responsible for this difference in the functioning of the ovary? The vagina and mammary gland under the influence of rabbit anterior pituitary behave in a manner similar to that which we observed after inoculation of guinea pig anterior pituitary. The uterus may show some proliferative activity in the mucosa connective tissue and in the glands; but the changes observed here are not quite so constant as those which occur in the vagina. It is of interest that in the vagina and cervix the stimulation is not limited to the epithelium but affects also the musculature, which undergoes mitotic proliferation. In general whenever marked growth processes are initiated in vagina and cervix, some proliferation seems to take place also in the musculature of these organs. In a case in which after 11 inoculations of one anterior pituitary, the interstitial gland predominated in the ovary, the vagina showed the structure which has been observed by us in pregnant and in hysterectomized guinea pigs.

In principle there is no marked difference between the effects of different quantities of rabbit anterior pituitary, but the larger quantities (two glands) produce more intense changes, while after inoculation of one-half a gland daily the effects are less intense and not quite so regular; for example, in one exceptional case in which after six inoculations of one-half of a rabbit gland the thyroid gland showed only a trace of hypertrophy, there were merely maturation processes noticeable in the ovary.

The thyroid gland undergoes a much more distinct hypertrophy after daily inoculation of one rabbit anterior pituitary than after daily inoculations of four guinea pig anterior pituitaries. However, the hypertrophy

caused by the rabbit anterior pituitary is definitely less marked than that caused by daily injection of 1 cc. acid extract of cattle anterior pituitary. A combination of daily injection of 1 or 2 cc. acid extract and of daily inoculation of one rabbit anterior pituitary intensifies the hypertrophy of the thyroid gland, and suppresses the growth and maturation promoting effects in the ovaries, which inoculation of the rabbit anterior pituitary alone would have exerted. However the latter asserts itself insofar as it may effect the production of large pseudolutein bodies, which acid extract of cattle anterior pituitary alone does not accomplish. Acid extract tends to induce in this combination, as well as if it is injected singly, the development of hypotypical follicles.

In three experiments in which we kept the anterior pituitary glands of rabbits previous to inoculation in a frozen state for from one to several days, it seemed that the growth promoting activity of the anterior pituitary was diminished, while the production of pseudolutein bodies and of interstitial gland was continued; also the hypertrophying effect of this material on the thyroid gland was quite marked. However, we consider it necessary to make additional experiments with frozen anterior pituitaries before we can state definitely that they differ in their effects from fresh glands.

III. INOCULATION OF ANTERIOR PITUITARY OF CAT

In this series the number of experiments was more restricted, only five experiments being carried out; the number of inoculations varied between three and six. In some experiments one, in others two glands were inoculated each day. The changes seen in the ovary of the immature guinea pig after inoculation with cat anterior pituitary are very similar to those seen after inoculation with rabbit anterior pituitary. In both cases growth impulses as well as a tendency to luteinization are transmitted to the follicles of the host. We notice thus the production of pseudolutein bodies, of theca interna as well as of granulosa origin. Vessels and connective tissue may grow into the granulosa of very large mature follicles. Furthermore the theca interna around atretic follicles may become hypertrophic and form interstitial gland; interstitial gland is also found in the medulla of the ovary. However, it seems that cat anterior pituitary has less power to induce proliferation and maturation of follicles than rabbit anterior pituitary and correspondingly a greater tendency to allow granulosa degeneration even of mature follicles. In the vagina we may find a very incomplete proliferation, and while the mammary gland showed proliferation in some cases, it was lacking in others. There may be thus a quantitative difference between the action of rabbit and cat anterior pituitary which can be largely overcome by inoculating two instead of one gland each time. However, considering our restricted number of experiments with cat anterior pituitary, we must leave the determination of possible finer differences in the effects of different quantities to future investigations.

As to the effects of cat anterior pituitary on the thyroid glands of the guinea pig, it produced hypertrophic changes, but they were relatively slight, and on the whole much colloid was retained in the thyroid acini. In one experiment in which the gland had been kept below freezing temperature for one or more days, the hypertrophy happened to be more marked. In individual cases there was no definite correspondence between the intensity of the thyroid hypertrophy and the amount of interstitial gland and pseudolutein tissue in the ovary which we found at the conclusion of the experiment.

IV. ADMINISTRATION OF VARIOUS PREPARATIONS OF ANTERIOR PITUITARY OF CATTLE

(a) *Injection of acid extracts from cattle anterior pituitary.* We have described the preparation of this extract previously. Daily intraperitoneal injections of 1 to 3 cc. of extract cause a rapid atresia in the majority of follicles, the intensity of this change depending upon the dose administered and on the length of time during which it is given. The period of administration varied between one day and two months. The effects of long continued injections will be described in a subsequent publication. If the action is pronounced only the granulosa of a few small follicles is preserved, while all the other follicles are atretic. In addition acid extract causes, in many cases, the formation of interstitial gland, which may be noticeable also in the medulla of the ovary, as well as of theca interna pseudolutein bodies of various sizes; usually the latter are small, but they may be large, if they are derived from large follicles which become atretic. In the latter case it is possible that some remnants of granulosa which escaped degeneration may participate in the luteinization process. While the atresia of follicles leading to a hypotypical condition of the ovaries is always present, formation of interstitial gland or of pseudolutein bodies may in some cases be lacking; either the former or the latter or both may be absent. The vagina is typically found in a quiescent state, consisting of one layer of very vacuolar mucoid cells resting on a layer of flat cuboidal cells. Often large vacuoles caused by degenerative processes in the mucoid epithelial cells develop between these two layers of cells. The mammary gland is either resting or shows only very slight proliferative activity. As we have described previously, the thyroid gland of the guinea pig is very strongly stimulated by intraperitoneal injections of acid extract. The hypertrophy and hyperplasia of the acinus epithelium is accompanied or followed by partial or almost complete solution and absorption of the colloid and, as Siebert and Smith (4) have shown, also by a marked stimulation of the basal metabolism; the latter is, however, prevented by previous extirpation of the thyroid gland. The hypotypical condition of the ovaries depends probably to a large extent upon the relative undernourishment caused by the rise in basal metabolism; but even in cases in which at early stages of the administration of acid extract there

has not yet been any noticeable loss in weight, the hypotypical changes may already be quite pronounced. It is therefore possible that the acid extract of anterior pituitary may in addition directly produce hypotypical changes in the ovaries. In renewed control experiments, in which we reduced the weight of guinea pigs by underfeeding, the hypotypical condition produced in the ovaries was apparently less pronounced than that observed after injection of acid extract. Of course the formation of interstitial gland and of theca interna pseudolutein bodies are due not to undernourishment, but to the action of the extract. The active principle present in the acid extract of cattle anterior pituitary has therefore effects on the ovary which are the opposite of growth production and maturation of the follicles. It never has the latter effect, nor does it cause ovulation. Alkali extracts of anterior pituitary seem to act in every respect like acid extracts on sex organs as well as on thyroid gland.

(b) *After extraction of powdered cattle anterior pituitary with weak acetic acid, the residue was dried and solid flakes of material were thus obtained.* Small pieces of this material were softened through immersion in sterile 0.9 per cent NaCl solution and then inoculated subcutaneously into guinea pigs; each time several pieces were introduced through a trocar. The number of inoculations varied in different experiments between three and ten, as a rule one inoculation being given daily. The guinea pig experienced either a slight loss or a slight gain in weight during the period of the experiment.

The effects on thyroid and sex organs were essentially similar to those observed after injections of acid or alkali extracts of cattle anterior pituitary. In the first few days an acute degeneration of the granulosa, affecting not only the large and medium-sized, but also some of the smaller follicles, initiated a marked hypotypical condition of the ovaries, with or without a subsequent formation of larger or smaller pseudocorpora lutea, mainly through hypertrophy of the theca interna, although it is possible that in some cases parts of the preserved granulosa may have participated in this process. Also interstitial gland formed in some cases. The vagina, uterus and mammary gland also behaved in a manner similar to that observed after injection of acid extracts. The thyroid gland showed definite hypertrophy, which was however not so marked as after injection of the extracts; there was also usually more solid colloid retained in the thyroids of guinea pigs into which the residue had been inoculated. Evidently a certain amount of the same principle that is active in the extract is retained in the residue and becomes effective after subcutaneous inoculation.

(c) *Twenty-five guinea pigs were inoculated with larger or smaller pieces of anterior pituitary gland of cattle.* In one series three or four pieces with an approximate diameter of 3 mm. were inoculated daily; in a second series, two pieces each with an approximate diameter of 1 mm.

were inoculated. The number of inoculations varied between five and 12. When the larger quantities were inoculated, the results were similar to those seen after inoculation of residue or after injection of acid extract. A hypotypical condition of the ovaries developed, which was however not always so pronounced as after injection of acid extract, and in the majority of cases theca interna lutein bodies of various sizes formed from follicles during early or late stages of connective tissue atresia; it is possible that in some larger bodies of this kind remnants of granulosa participated in their formation; also some interstitial gland could develop but was usually not prominent. Vagina and mammary gland were in a quiescent state. The epithelium of the former consisted of a cylindrical mucoid layer resting on a layer of flat cuboidal cells. The condition of the uterus showed certain slight variations which were also found in other series of experiments and the cause of which is not yet quite definite. The thyroid glands showed hypertrophy which was however not quite so marked as after injection of acid extract; in particular the amount of colloid retained was somewhat greater. In the majority of cases glands which had been kept from one to several days on ice were inoculated; but in other cases material obtained from cattle one to two hours previous to inoculation was used. The results were the same in both cases. In no instance did inoculation with this material promote the growth of the follicles; there was on the other hand again a distinct relation between the intensity of follicular atresia, of loss of weight and of hypertrophy of the thyroid gland.

In case of inoculation of small pieces of anterior pituitary, the effects on thyroid and sex organs were still more moderate. In a number of cases lutein bodies developed from theca interna of follicles during atresia; it is possible that follicles which approached maturation may in these cases have led to the formation of granulosa pseudolutein bodies. In other cases these structures were lacking. The hypotypical condition of the ovaries was on the whole less pronounced than after inoculation of larger pieces; in some cases where there was gain in weight, it was entirely absent and there was correspondingly almost complete lack of thyroid hypertrophy. On the other hand, there was no indication of acceleration of the growth of follicles and of the maturation of large follicles, such as we found after inoculation of guinea pig, rabbit and cat anterior pituitary. In case large follicles were present, and especially if they approached maturation, a partial proliferation of the vagina occurred; usually, however, it was in a resting stage. In one exceptional case an ovulation did occur with the corresponding changes in vagina and uterus.

In evaluating the results obtained with the various preparations of cattle anterior pituitary, we must consider the fact that in preparing 1 cc. extract from anterior pituitary of cattle a much larger quantity of gland tissue is used than that used for subcutaneous inoculation of pieces of gland.

(d) In a number of experiments we tested the effects of ether or petroleum ether extracts of anterior pituitary of cattle gland. After evaporation of the extractive the residue was emulsified with lecithin and daily injections of this emulsion were made. There was no noticeable effect on the thyroid gland nor on the ovaries.

V. INJECTION OF URINE OF PREGNANT WOMEN.

It has been found first by Aschheim and Zondek and subsequently by others that in urine of pregnant women a substance is present which has an effect similar to that exerted by anterior pituitary gland. It was therefore of interest to compare the effect of injections of such urine with that of the various anterior pituitary preparations on the sex organs and thyroid gland of immature guinea pigs. The conclusions at which we arrived are based on a microscopic study of the sex organs and thyroid glands of 41 guinea pigs injected with amounts of urine varying between 1 and 4 cc. daily during periods varying between one and 21 days. The effects which we noticed are, on the whole, intermediate between those observed after inoculations of rabbit or cat anterior pituitary and after injection of extracts of cattle anterior pituitary. They resemble those following rabbit anterior pituitary inoculations, insofar as both granulosa and theca interna lutein bodies and interstitial gland are produced and as there is a tendency for the granulosa of still growing small or medium follicles to undergo premature maturation, which is, however, usually not complete; furthermore, in both cases we observed that an ingrowth of connective tissue and capillaries may take place from theca interna into the granulosa, in instances in which the greater part of the latter is still preserved, as well as in instances in which the granulosa has partly undergone degenerative changes. A further point of resemblance is that in later stages the development of interstitial gland may predominate, occupy the greater part of the ovary and exert pressure on the growing follicles. On the other hand, the effects of injections of urine of pregnant women resemble those noticed after injection of acid extract, inasmuch as in both cases atretic processes predominate, combined with a tendency to formation of hypertrophic theca interna. Thus theca interna lutein bodies are produced from follicles during the process of atresia, and interstitial gland from the theca interna around completely atretic follicles and apparently also from the tissue surrounding the vessels in the medulla of the ovary; it is moreover possible that the latter tissue likewise was originally derived from theca interna. Furthermore, the effects resemble those observed after injections of acid extracts of cattle insofar as in both cases there is lacking the accelerated production of large mature follicles which is so pronounced after inoculation of rabbit, cat and also of guinea pig anterior pituitary; instead we find a tendency to the production of atretic follicles in combination with luteinization processes. The latter are, however, as far as luteinization in the granulosa as well as in the theca interna is concerned,

much more pronounced after injection of urine than after injection of acid extract. Neither after injection of acid extract nor after inoculation of rabbit or cat anterior pituitary, nor after injection of urine does ovulation, as a rule, occur.

The effects of urine on the vagina are similar to those observed after inoculation of rabbit anterior pituitary; there is in most cases a partial proliferation of the vaginal epithelium, which is more marked after inoculation of rabbit, cat and guinea pig anterior pituitary than after urine injection. In the latter case the stimulating effect on the vagina may be very slight or almost lacking. In this respect, therefore, the effects of urine injections are again intermediate between those induced by acid extracts and by inoculations of anterior pituitary of the animals mentioned. However, at a later stage of the injections of urine, when the ovaries have largely been converted into interstitial gland, the vagina may assume the character found in pregnant and hysterectomized animals: cylindrical epithelium of an extremely mucoid character standing on a layer of flat cuboidal epithelium. The mammary gland varies; in some cases it may be in a state of active proliferation similar to that produced by anterior pituitary of rabbit or guinea pig; in others it may be inert or almost inert, as it is after injection of acid extract of anterior pituitary of cattle; also the effects on the uterus are somewhat variable. While thus the reactions of the sex organs in the immature guinea pig are intermediate between those following rabbit anterior pituitary inoculation and administration of cattle anterior pituitary preparations, the thyroid of the immature guinea pig behaves towards injections of urine of pregnant women approximately as it does towards inoculations with anterior pituitary of guinea pig; both are inert or almost so as far as their effect on the thyroid gland is concerned. However, while the guinea pig anterior pituitary may in some cases call forth at least a very slight and usually locally restricted hypertrophy, the urine of pregnant women is entirely inert. There may possibly have been elicited, in a few cases, a trace of a reaction; but even this is doubtful. On the other hand, we can show that urine does not contain a substance which prevents hypertrophy of the thyroid gland, by combining injections of urine of pregnant women with intraperitoneal injections of acid extract; the latter are able to call forth hypertrophy of the thyroid gland notwithstanding the simultaneous injections of urine. Such combinations may call forth in the ovaries the production of interstitial gland and of theca interna lutein bodies. We tested the effect of urine on the thyroid gland during the early winter months of 1930/31 at a time therefore when the thyroid gland is in a much more responsive state to factors which tend to call forth hypertrophy than it is during the summer months; nevertheless the hypertrophy was lacking.

DISCUSSIONS AND CONCLUSIONS

From these investigations it follows that anterior pituitary preparations from different mammalian species differ from one another in their

effects on sex organs as well as on thyroid gland of the immature guinea pig. If we compare the actions of various anterior pituitary preparations on the ovary we can arrange the glands from different species in the following order: (1) Anterior pituitary of guinea pig; (2) of rabbit and cat; (3) urine of pregnant women; (4) various anterior pituitary preparations from cattle (pieces of cattle gland, acid as well as alkali extracts and residue). The order indicates a decreasing tendency to promote growth and an increasing tendency to promote the development of theca interna lutein bodies and of interstitial gland in the absence of growth promoting functions; in the intermediate types (2 and 3) we find in addition a pronounced tendency to cause maturation of the granulosa which may extend even to smaller follicles, while in (1) the tendency to maturation affects merely the granulosa of very large follicles which would naturally undergo maturation. (2) and (3) differ, inasmuch as in (2) we find a definite tendency to accelerate the growth of follicles, while in (3) this tendency, if present at all, is inconsiderable or not manifest.

If we arrange these preparations in accordance with their effects on the thyroid gland of the immature guinea pig the order is as follows: (1) Acid and alkali preparations and, to a less extent, pieces of gland and residue after extraction of anterior pituitary of cattle, (2) rabbit, (3) cat, (4) guinea pig, (5) urine of pregnant women. The order corresponds to a decreasing hypertrophy, (1) causing the greatest, (5) the least and (4) almost as little hypertrophy of the thyroid gland as (5). We have to consider in this case the complication that in (1) the amounts of the various cattle anterior pituitary preparations which we administered differed in the quantity of the substance causing hypertrophy of the thyroid gland. Likewise the quantity of one anterior pituitary of guinea pig is less than that of one anterior pituitary of cat or rabbit; furthermore, the quantity of cattle anterior pituitary preparations administered is, on the whole, greater than that of guinea pig, rabbit and cat.

The difficulties in interpretation arising from these differences in absolute quantities can to some extent be overcome (a) by varying the quantities of anterior pituitary used in each species and determining the influence of these variations on the effects exerted by these preparations; (b) by comparing the action on thyroid gland with that on the sex organs of the guinea pig and thus obtaining a standard of the efficiency of the material administered.

In interpreting these facts we have to consider three possibilities. (1) There may be one active principle in the anterior pituitary responsible for all the changes observed in sex organs and thyroid of the guinea pig. If present in small quantity this substance accelerates the growth of follicles. As soon as follicles have reached large size, they mature and ovulation occurs. Mature follicles which do not rupture may be converted into large granulosa lutein bodies. If present in larger quantity this substance does not induce rapid growth of follicles, maturation and rupture of large

follicles, but instead it accelerates atresia of follicles, and accompanying atresia it causes hypertrophic and hyperplastic changes in the theca interna and leads to the production of theca interna lutein bodies and interstitial gland. In addition in small or medium-sized growing follicles the granulosa may prematurely mature and thus a premature aging may take place, and the theca interna may hypertrophy around such growing follicles. The anterior pituitaries of different species differ in the amount of this substance which they contain. Only if larger quantities of it are present does the thyroid gland become hypertrophic. (2) There may at least be two active substances present in the anterior pituitary, one of them causing growth, maturation and rupture of large follicles, and the second causing the changes mentioned in the sex organs as well as hypertrophy of the thyroid gland. In different species these two substances are present in different quantities. Thus in the anterior pituitary of the guinea pig the growth-promoting substance greatly predominates, while in cattle anterior pituitary the second substance is the dominating one. In urine of pregnant women also a substance is present which induces luteinization processes. (3) There exists the possibility that the effects called forth by the anterior pituitaries of different species depend not only upon the character of the species from which the anterior pituitary has been taken, but also upon the character of the species which serves as a test organism.

We have seen that we can intensify the effects characteristic of each species by using larger quantities of the various pituitary substances; but so far we have not succeeded in abolishing the differences observed in different species through varying the amounts used. By diminishing the quantities of anterior pituitary of cattle we could not obtain the effects of guinea pig anterior pituitary, and not even those of rabbit or cat anterior pituitary as far as the action on sex organs is concerned. Conversely by increasing the quantity of guinea pig or of rabbit or cat anterior pituitary we did not approach the effects produced by cattle anterior pituitary. Furthermore by increasing the quantity of guinea pig anterior pituitary we were not able entirely to initiate the action of rabbit anterior pituitary nor could we, by reducing the latter, initiate ovulation, although rabbit and guinea pig anterior pituitary are related to each other in their action in certain respects more than the same glands in other species. However, in one case in which we reduced the quantity of rabbit anterior pituitary, we obtained the growth-promoting effect without luteinization, but no ovulation took place. It is only through inoculation of guinea pig anterior pituitary that we were able to obtain ovulation. Variation in the quantity of urine injected did not essentially change its characteristic effects.

There remains the possibility that the delay in inoculating anterior pituitary of cattle after the death of the animal is responsible for the distinctive effects produced by this preparation; however, we found that even if we inoculated relatively fresh pieces of cattle gland, the results were the same as those obtained after inoculation of gland material that had been

kept on ice for a day or longer. Likewise our experiments with guinea pig anterior pituitary show that it does not need to change its character or lose materially in strength, when kept in a frozen state for several days previous to inoculation. On the other hand, a few experiments with rabbit and cat anterior pituitary indicate that possibly the growth-promoting effect of anterior pituitary substance decreases, if the gland is kept frozen for one or more days. However, it will be necessary to extend the latter experiments before a definite conclusion can be reached as to the effect of freezing. We conclude, therefore, that while our results indicate that differences in the quantities of the different kinds of glands used play a certain role in explaining the differences in the action of the latter, we cannot attribute these differences entirely to this factor. But, whether the second or third interpretation applies or whether both of these apply, this remains still to be determined. As far as the atresia of the follicles, which is induced especially by the administration of anterior pituitary of cattle, is concerned, there is no doubt that it is in a large part due to the increased activity of the thyroid gland, which itself is an effect of the inoculation of anterior pituitary. In so far the atresia of follicles would therefore represent an indirect effect of the anterior pituitary. However, it is possible that the cattle anterior pituitary may promote also directly the atresia of follicles, because we noticed this effect after administration of cattle anterior pituitary even in cases in which there was not yet any noticeable loss in weight at the time of examination.

We have stated that it is only after inoculation of guinea pig anterior pituitary that we have obtained in the immature guinea pig accelerated ovulation in a considerable number of cases. If in experiments with material from other species we obtained ovulation at all, it was certainly an exceptional occurrence. Now, inoculation of guinea pig anterior pituitary is characterized by marked acceleration of follicular growth and maturation of full-sized follicles, combined with a minimum development of interstitial gland and a minimum formation of lutein bodies, especially of theca interna origin. This suggests that possibly lutein bodies and interstitial gland may inhibit ovulation in a similar way to corpus luteum, which organ, as we in our earlier experiments have shown, has such an inhibiting effect. (5) In this connection it is of interest that according to Allen (6) inoculation of monkey anterior pituitary in the monkey produces ovulation, while dog anterior pituitary was found to be inert.

In regard to the behavior of the vagina, we can summarize our observations as follows: There is a correspondence between the development of the follicles and the proliferation of the vaginal epithelium. If large follicles develop without the presence of inhibiting factors an incomplete growth in the vagina may occur. This may even take place in normal young, as yet immature guinea pigs. The full development of the corpus luteum represents an inhibiting factor, as Loeb (7) and Loeb and Kountz (8) have shown. Also during the normal cycle a proliferation of the

vagina does not take place, notwithstanding the presence of mature follicles, until the corpus luteum has begun to retrogress and the next ovulation is imminent. Administration of those anterior pituitary preparations which cause development of hypotypical follicles with or without production of interstitial gland or theca interna lutein bodies, leads to inactivity in the vagina. (Effect of extracts of anterior pituitary of cattle.) The presence of mature follicles in combination with interstitial gland or with lutein bodies leads usually to an incomplete proliferation of the vagina. The presence of mature follicles, not associated with the formation of interstitial gland or lutein bodies, and especially the presence of these structures directly preceding ovulation lead to a full proliferation of the vagina with the production of keratin. Injection of urine of pregnant women causes a very slight proliferation of the vagina, presumably due to the presence of Theelin and Theelol [Doisy and associates (9)] in such urine. In cases in which so pronounced a development of interstitial gland had occurred in the ovary that it occupied the greater part of this organ there was found a condition in the vagina similar to that observed in pregnant and in hysterectomized guinea pigs (7), where an excess of mucoid is produced in the large cylindrical surface cells of the epithelium which exerts pressure on the layer of flat epithelial cells underneath. Such changes were noticed after about 20 days, when urine was injected daily and also after long continued inoculations of rabbit anterior pituitary.

These observations suggest that not only corpus luteum, but also interstitial gland and lutein bodies may possibly exert an inhibiting effect on the vagina. However, it will be necessary to study further the variable efficiency of mature follicles in setting free the growth-promoting factors acting on the vagina under different conditions. It may be remarked that the stages intermediate between full proliferation and a resting condition, which we have described, would have escaped recognition, if we had relied merely on the use of vaginal smears.

As to the proliferation of the mammary gland it is usually associated with a full development of mature follicles. The behavior of the uterus varied somewhat under different conditions and needs further experimental analysis.

There still remains the question as to the relation between the changes observed in the sex organs and in the thyroid gland after administration of anterior pituitary preparations. We can state definitely that there exists no connection between the promotion of follicular growth in the ovaries and hypertrophy of the thyroid gland; but there exists a certain parallelism between the tendency of certain anterior pituitary preparations to inhibit full growth of the follicles and to intensify follicular atresia, to produce theca interna lutein bodies and interstitial gland on the one hand, and to induce hypertrophy of the thyroid gland on the other. This parallelism suggests that the substance causing thyroid hypertrophy and that causing luteinization of the ovary are identical. Apparently contradictory

to this conclusion is the lack of the urine of pregnant women to cause thyroid hypertrophy, although it causes luteinization. In this connection we considered the possibility* that in this urine a substance is present which antagonizes the effect of anterior pituitary on the thyroid gland—but our experiments have shown that this is not the case—or else that the active substance in the urine which acts on the ovary is different from the active substance present in the anterior pituitary gland. Otherwise we would have to conclude that the parallelism between the luteinizing effect on the ovary and the hypertrophic changes in the thyroid gland is merely a coincidence. Although the recent experiments of Reichert, Pencharz, Simpson, Meyer and Evans (10), which showed that, in the dog, urine of pregnant women becomes ineffective after hypophysectomy, are in harmony with our assumption that the substances active in urine of pregnant women and in anterior pituitary are not identical, still we do not at present wish to exclude the possibility that the action on thyroid and the luteinizing effect on the ovary are due to different substances. Both interpretations are possible.

SUMMARY

Samples of anterior pituitary substance from different species of mammals as well as of urine of pregnant women differ from one another in their effects on sex organs and thyroid gland of immature guinea pigs; these effects in the case of each species are specific. We have discussed the possible interpretations of these observations which are more readily compatible with the view that at least two constituents of the anterior pituitary are responsible for these effects, than that the latter are attributable to the action of different quantities of one and the same substance, and that in these different species these two substances are distributed in different proportions. In the guinea pig only guinea pig anterior pituitary seems as a rule to be able to induce ovulation. We recognized intermediate states of proliferation of the vagina which occur under the influence of large growing or mature follicles under certain conditions; there is some indication that the interstitial gland and theca interna lutein bodies, if present in sufficient quantity, may exert functions similar to that of the corpus luteum and, under certain conditions, inhibit ovulation and full proliferation of the vagina.

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THE EFFECTS OF DIETARY DEFICIENCY OF IODIN UPON THE THYROID AND PARATHYROID GLANDS IN THE RAT

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There is still difference of opinion concerning the relation between goiter and dietary deficiency of iodin. The literature on the question has been reviewed by Jackson (1, 2) and more recently by Hellwig (3, 4). The production of goiter in rats by low-iodin diets has been claimed by Hayden, Wenner and Rucker (5), Tanabe (6), and Krauss and Monroe (7). On the other hand, Hellwig (3, 4) has recently obtained only negative results. Further study of the question therefore appears desirable. The present experiments extended over a considerable period of time, with careful attention to the diet and to the technique of determining the effects upon the size and structure of the thyroid gland. Observations were made also upon the parathyroid glands.

MATERIALS AND METHODS

The rats used were of the Wistar albino strain, reared in the colony maintained in our laboratory. Two litters including 12 animals were divided into four groups of three rats each. Two of these groups (male and female) were test rats, placed on the low-iodin diet; with two corresponding control groups on the same diet plus iodin. Litter-mates were distributed between the test and control groups.

We are indebted to Professor George O. Burr for advice as to the diet used. The basal ration was his diet 550B, containing purified casein, 12 per cent; McCollum salt mixture 185, 4 per cent, and sucrose, 84 per cent. Distilled water was supplied *ad lib.* in glass bottles with tubular glass outlets. The accessories, fed separately every day, for each rat, were as follows: dried brewer's yeast, 0.75 gram; "AD" (concentrated extract of cod liver oil), 2 drops; "E" (concentrated extract of wheat germ), 2 drops; corn oil, 15 drops. This constituted a diet extremely low in iodin content, but complete and adequate in all other respects, so far as known.

For the control rats, the diet was the same as above, except that 1⅓ milligram of potassium iodid was added to each liter of the distilled water furnishing one milligram of iodin per liter of water. This was estimated to be sufficient for a normal iodin intake.

The experiment began in April, 1930, when the rats were weaned at 3 weeks of age, and continued until November, 1930, when they had reached practically the adult stage at about 8 months of age. Each group of three rats was kept in a separate cage. Body weights were noted weekly for each individual animal. The food and water consumption also was care-

fully measured and recorded for each of the four groups. The methods were the same as those used by Jackson and Smith (8).

At the close of the experiment the rats were killed with chloroform and a complete autopsy was made, with observations on the appearance and weights of the various organs. The thyroid gland was exposed and inspected, but it was not weighed. Our previous experience indicated that gross weights of the thyroid are of doubtful validity, due to its small size, delicate texture and difficulty in dissection. On account of its irregular form, measurements of the diameters are also unreliable. In this study the gland was fixed *in situ* with the larynx and adjacent trachea in Zenker's fluid, embedded in paraffin and cut in serial sections at 5 or 6 microns in thickness. After staining, every tenth section of the thyroid was outlined on uniform paper, using the Edinger projection apparatus with known magnification. From the weight of a measured area of the paper, it was easy to calculate the volume of the gland from the weight of the paper outlines. The volume of the corresponding pair of parathyroid

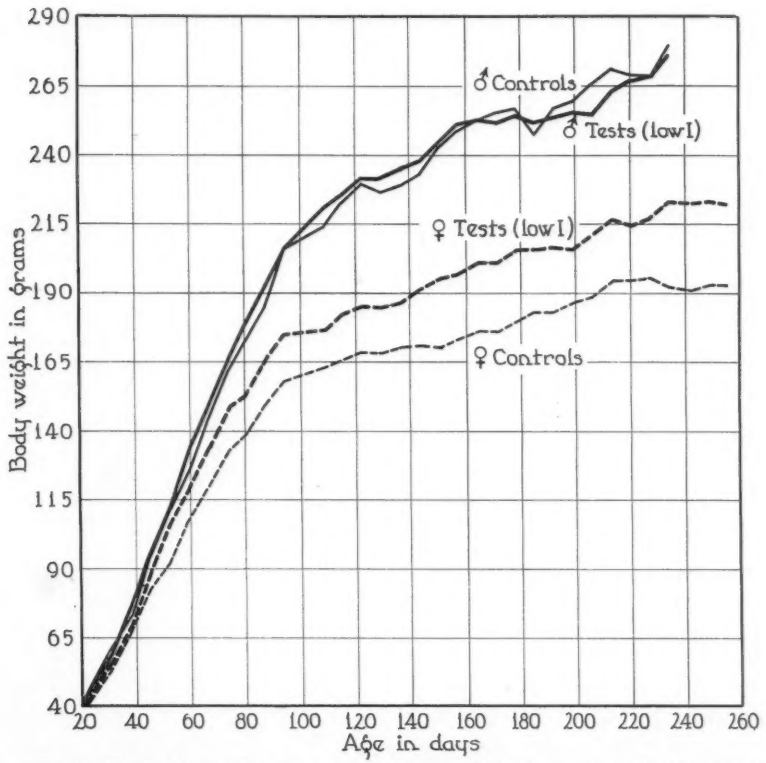

Fig. 1. Chart showing the average growth curves of the four groups of rats: male test rats (low-iodin diet), male controls, female test rats (low-iodin diet) and female controls. The male rats show no difference in growth, and the slightly higher body weight of the female test rats is probably insignificant.

glands was similarly calculated. Unfortunately the serial sections were incomplete in some cases. Complete sets of sections of the thyroid gland were available in only eight, and of the parathyroid in 11 of the 12 rats used.

OBSERVATIONS AND CONCLUSIONS

General Condition and Body Weight (Fig. 1). All the rats remained healthy and vigorous throughout the experiment, with no apparent difference between the test rats on low-iodin diet and the controls. As shown by the growth curves, the male rats grew steadily from an average initial weight of about 40 grams (at 3 weeks) to about 280 grams at 235 days of age, with no appreciable difference between test and control animals. The female rats, with similar initial weight, reached an average of about 195 grams in the control rats and 220 grams in the test rats on low-iodin diet. The higher average of the female test rats is of doubtful significance. In general, the growth of all these rats is fully equivalent to the Wistar albino norm of Donaldson (9), and gives no evidence of any thyroid disturbance.

Consumption of Food and Water (Table I). In general, after the first month of experiment the daily average amount of food and water consumed per rat remained fairly constant, although in general with increasing body weight the amount per gram of rat decreased. The higher room temperatures in July and August made less disturbance than might be expected.

TABLE I

DAILY AVERAGE FOOD AND WATER CONSUMPTION IN EACH GROUP
Food in Grams, Water in Cubic Centimeters.

	April	May	June	July	August	September	October
MALE TEST							
Food per rat	6.4	9.7	9.5	10.7	8.6	8.8	10.7
Food per gram rat	.094	.070	.048	.047	.035	.035	.042
Water per rat	8.5	12.4	14.7	17.4	13.6	12.7	12.6
Water per gram rat	.119	.082	.071	.075	.054	.050	.047
MALE CONTROL							
Food per rat	8.0	10.4	11.0	10.6	9.3	10.0	11.4
Food per gram rat	.117	.076	.057	.048	.039	.039	.043
Water per rat	7.9	10.0	12.7	15.2	13.6	12.4	11.4
Water per gram rat	.113	.068	.062	.067	.054	.049	.043
FEMALE TEST							
Food per rat	7.3	9.9	8.4	9.0	7.2	9.0	9.5
Food per gram rat	.113	.079	.050	.049	.038	.044	.045
Water per rat	8.5	10.9	12.8	12.5	12.4	11.9	11.8
Water per gram rat	.128	.080	.074	.068	.063	.058	.054
FEMALE CONTROL							
Food per rat	6.3	9.1	7.9	8.3	6.4	7.5	9.4
Food per gram rat	.104	.080	.052	.050	.037	.042	.049
Water per rat	7.9	12.0	13.5	13.6	13.5	13.0	12.6
Water per gram rat	.125	.094	.087	.081	.078	.071	.065

Of the male rats, the control animals averaged slightly higher in daily consumption of food, both per rat and per gram of rat. However, this is probably not due to the iodin in the diet of the control rats, since this difference in food consumption did not occur in the females on the same diets.

The consumption of water is of especial interest, since it enables us to calculate the iodin-intake. Among the male rats, the daily water-intake (in contrast to the food-intake) averaged slightly but almost constantly lower in the controls than in the test rats, both per rat and per gram rat. Among the females, however, the reverse holds true after the first month, so that the difference is of doubtful significance.

For the entire period, the water consumption per 100 grams of rat averaged 5.91 cc. daily for the control males, 6.53 cc. for the test males, 8.20 cc. for the control females, and 7.63 cc. for the test females. Averaging the data for both sexes gives a general average of 7.05 cc. daily per 100 grams of rat for the controls, and 7.08 cc. for the test rats on low-iodin diet. For the control rats, this corresponds to a daily iodin intake of 0.007 milligram of iodin. This happens to be the exact amount estimated by Mendel and Vickery (10) in an average daily food intake of 7 grams per rat for the unsupplemented conventional diets, including 4 per cent of the Osborne-Mendel salt mixture (which contains 0.0032 per cent of potassium iodid).

Appearances at Autopsy. At the end of the experiment, the rats were killed and carefully autopsied. They were found to be in good condition throughout, with no noteworthy abnormality in the weight or appearance of the skin or other organs in either the test rats or the controls. The thyroid gland in all cases appeared within the normal range of size, and showed no indication of abnormal enlargement.

Size and Structure of the Thyroid Gland (Fig. 2). As shown in the field graph, complete volumetric data were available for the thyroid gland

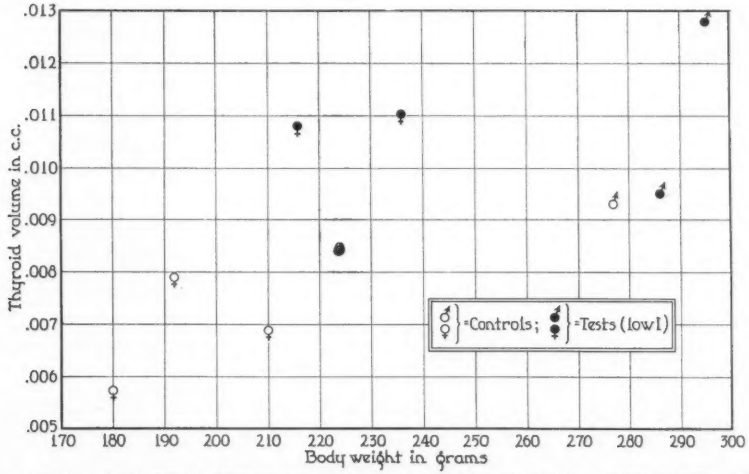

Fig. 2. Field graph showing the volumes of the thyroid glands plotted against body weight in each case. The volume appears somewhat greater in the test rats (low-iodin diet), but the body weight is also greater in these test rats, and the apparent enlargment of the thyroid gland is probably insignificant.

in three males and five females. Of the three males, the gland in one control measured 0.0093 cc. and in the two test rats 0.0095 and 0.0128 cc., respectively. Of the five females, the volumes in the three controls were 0.0058, 0079 and 0.0069 cc., and in the two test rats 0.0108 and 0.0111 cc., respectively. These volumes appear higher in the test rats, but it is further evident that the body weights also are somewhat greater in these test rats. This makes it more difficult to judge as to relative enlargement of the glands.

In cases like this, where test animals and controls differ in body weight, it is useful to compare each individual gland with Donaldson's norm for rats of the same body weight. Assuming the equivalence of volumes in cubic centimeters, and weights in grams, it is found that all the thyroid glands in our series are far below Donaldson's norm. The figures for the three female controls are —81, —75 and —79 per cent; for the female test rats —68 and —70 per cent; for the male control —78 per cent, and for the male test rats —78 and —71 per cent, respectively.

These low figures for the thyroid gland in our series are to be expected for two reasons. In the first place, the Wistar norm for the thyroid is admittedly too high. King and Donaldson (11) state that (in 1929) the observed values for albino thyroid are 52 per cent below the reference table values for the males, and 53 per cent below for the females. This would account for most of the apparent subnormality in our series. The remainder is doubtless due chiefly to the well-known shrinkage caused by the process of histologic fixation and paraffin embedding of the glands.

Although the shrinkage affects the absolute size of the glands, they are still comparable with each other, since presumably all were affected alike by the process. From the figures above mentioned it appears that (combining sexes), the thyroid glands in the four control rats averaged 78 per cent below the Wistar norm, while those in the four test rats averaged only 72 per cent below. The difference of 6 per cent is certainly insignificant, considering the normal variability of the thyroid and the relatively small number of animals used.

While the results are thus inconclusive, they confirm those of Hellwig in indicating no appreciable thyroid enlargement on a very low-iodin diet over a relatively long period of time. Certainly there is nothing approaching the doubling in thyroid weight found by Hayden, Wenner and Rucker (5) in rats after only 4 weeks on a low-iodin diet. Such enlargements are apparently due to something other than a deficiency of iodin-intake. Hellwig supports the theory that an excess of calcium may be an important factor in thyroid hyperplasia.

In each of the 12 rats, the sections likewise revealed no constant or significant difference between the test animals and controls in histologic structure of the thyroid glands. All showed the typical thyroid structure as described by Jackson (12), with no indications of either atrophy or hypertrophy of the gland.

Size and Structure of the Parathyroid Glands (Fig. 3). Jackson (12) made some observations on the parathyroid glands of the rat during general inanition, but apparently no studies have been made on these organs during iodin-deficiency. The field graph shows the volumes of the parathyroid (pairs) in the 11 cases, including three control females, two test females, three control males and three test males. While there is some individual variation, there is clearly no significant difference in parathyroid size between the test and control animals.

However, since these are apparently the first volumetric data on the parathyroid glands, it may be desirable to point out the marked sex difference in their size. The average of 0.00038 cc. for the five females is abso-

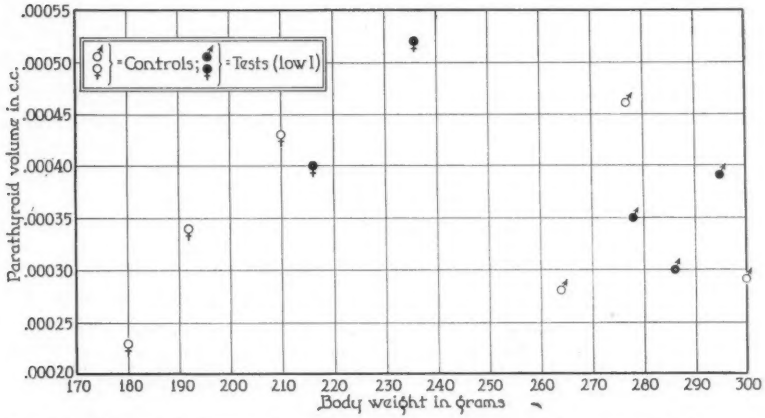

Fig. 3. Field graph showing the volume of the parathyroid glands (pairs combined) plotted against the body weight in each case. There is no significant difference in size between the test rats and controls. In general, the parathyroid glands in the female rats appear relatively larger in proportion to the body weight.

lutely greater than that of 0.00035 cc. in the six males, in spite of the difference in body weight, which averages 283 grams in the males and only 207 grams in the females. In the three males for which both thyroid and parathyroid volumes were available, the parathyroids averaged 3.7 per cent of the thyroid volume (latter including the parathyroids also). The range was from 3.0 to 5.0 per cent. In the five females, the parathyroids averaged 4.6 per cent of the thyroid volume (range 3.7 to 6.3 per cent). This confirms the discovery of Jackson (12) that the parathyroid glands are relatively larger in the female rats. A similar sex difference in the size of the hypophysis and suprarenal glands in the rat is already well known and clearly established.

Histologically, the parathyroid glands in the present series appeared entirely normal, with no sex difference in structure and likewise no difference between the test rats and the controls.

SUMMARY

Six Wistar albino rats (three males and three females) were reared from weaning until adult on a very low-iodin diet. A corresponding number of litter-mate controls were reared on the same diet plus an estimated normal supply of iodin.

All the rats remained healthy and grew normally, with no significant difference between test rats and controls in food-intake, water-intake, or body weight.

Since the weights and usual measurements of the thyroid gland in the rat are considered as somewhat unreliable, the more laborious but accurate method of volumetric determinations from serial sections was used. No appreciable enlargement of the gland was found as a result of the low-iodin diet, and no significant difference in histologic structure.

Likewise no significant difference was found between the test rats and controls in the size or structure of the parathyroid glands. A sex difference in these glands was confirmed, showing relatively larger size in the female rats, as is already well known for the hypophysis and suprarenal glands.

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WEIGHT OF GOLD FISH INFLUENCED BY TESTICULAR SUBSTANCE DIET

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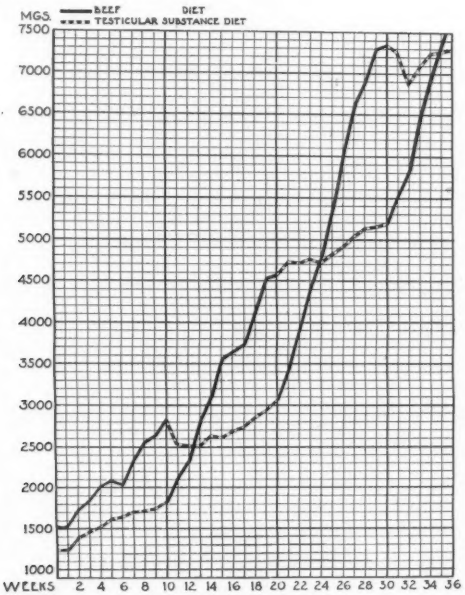
SAN QUENTIN

It has been found that goldfish, when fed on a diet of ground-up testicular substance from the ram, increase their activity by 400 per cent over that when fed on dried shrimp meat.*

Experiments were made to find out how the weight of the fish would be influenced by a diet of beef muscle as compared to ram testicular substance.

Into a bell jar No. 1 were placed two fish together weighing 1500 mgm. For ten weeks they were fed each week one-half their body weight of lean beef muscle in two feedings.

Into a second jar No. 2 were placed two fish together weighing 1250 mgm. These were fed weekly one-half their body weight of ground-up testicular substance in two feedings.



At the end of ten weeks those in jar No. 1, on lean beef muscle, had gained 1300 mgm., while those on the testicular substance, No. 2, had gained only 550 mgm.

*Activity of Goldfish on Testicular Substance Diet, This Journal, **15**: 55. 1931.

The groups were then reversed: Those in jar No. 1 were given testicular substance for ten weeks and those in No. 2 given beef.

At the beginning of the third ten weeks' period the fish were returned to the diet on which they had started the experiment.

Here again those on the beef, Group No. 1, gained 4300 mgm., while those on the testicular material, Group No. 2, gained 650 mgm. in the ten weeks' period.

The results are shown by the accompanying graph.

Knowing that the testicular diet increases the activity of fish, it might be inferred that the metabolism is increased.

Assuming comparable adequacy of the two diets *as food,* the differential growth effects could be ascribed to differences in expenditure as between the two functions.

This experiment might have some bearing on the cause and treatment of obesity. The results are suggestive of the common practice of animal husbandmen of castrating animals as a means of facilitating fattening.

SUMMARY

Goldfish fed on whole testicular substance did not increase in weight as much as did those fed on beef muscle.

A reversal of the diet of the two groups showed a slowing up of growth of those when fed the orchic substance.

This suggests that metabolism is increased by the testicular substance, previous work having shown a marked increase in muscular activity.

CORTIN IN A CASE OF POSSIBLE ADRENAL INSUFFICIENCY DURING PREGNANCY*

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AND
IRVING W. POTTER
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A condition which sometimes develops in pregnancy suggests adrenal insufficiency. One or more of the characteristic symptoms may be present, viz., asthenia, gastrointestinal upset and sometimes pigmentation. A very severe case which presented this picture came under the care of one of us. Treatment with Cortin was tried and the results were so striking that the case is herewith presented.

A housewife, aged 30, six months pregnant, was admitted to the Millard Fillmore Hospital because of weakness and vomiting which had been present for a considerable time. She was treated with fluids—glucose and salt solution by rectum, intravenously and subcutaneously. After two weeks she was discharged somewhat improved. Her weakness, however, became progressively worse and fainting spells occurred frequently. Her appetite was very poor. Her weight decreased from 160 to 105 pounds. A miscarriage had occurred during a pregnancy six years before.

Physical Examination showed an emaciated woman, with evidences of extreme muscular weakness. She was very nervous and excitable. Her face showed an anxious expression. Systolic blood pressure was 78 and diastolic 40. The heart rate was rapid. The nipples showed only normal pigmentation. There were, however, a few dark freckles on the arms. (These were said to have been present for a considerable time.)

Laboratory Findings: The Wassermann reaction on the blood serum was negative. Urinalysis gave normal findings. The red cell count was 3,864,000 and hemoglobin was 65 per cent. Blood urea was 140 mgm.

Management and Course: Cortin, 5 cc. daily subcutaneously, was started when the patient was seven and one-half months pregnant. Four days later the systolic blood pressure was increased to 90 and the diastolic 48 mm. Hg. After fifteen days of treatment the systolic blood pressure remained consistently at 95 mm. Hg. The patient stated that improvement had been remarkable. She could perform her household duties without interruption, whereas before treatment it was necessary for her to lie down frequently. The fainting spells and vomiting disappeared and her appetite became much better. The general nervousness and irritability were no longer evident and she was able to sleep well. She gaineed about fifteen pounds. The extract was administered for seventeen days. At full term

*Aided by a grant from the Ella Sachs Plotz Foundation.

she was delivered by Porro-Cesarian section. Her operative recovery was uneventful and she returned home in fifteen days. The baby was normal. Since her delivery her health has been excellent and there have been no further symptoms suggesting adrenal insufficiency.

SUMMARY

A case of late pregnancy with great loss of weight, extreme muscular weakness, low blood pressure and nervous symptoms was treated with Cortin. Blood pressure rose, muscular weakness and nervous symptoms largely disappeared, and the patient gained weight. At full term she was delivered by a Porro-Cesarian section. The child was normal.

QUININE AND IODINE IN EXOPHTHALMIC GOITER

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Iodine, and quinine in lesser degree, are credited with nullifying the symptoms of exophthalmic goiter through effects, directly or indirectly, upon the thyroid gland. Following their administration there is a change in the architecture of the organ. There is a marked accumulation of colloid with resulting compression upon and flattening of secreting cells lining the acini, a reduction of thyroid vascularity and usually a greater iodine storage. This resting stage of the thyroid is associated with an abeyance of many of the constitutional symptoms. There is a reduction in metabolic and pulse rate, an increase in weight, improvement in well being, and the general appearance of remission or approaching recovery from the disease.

In the average case of exophthalmic goiter iodine may produce startling benefit within a week or two after its administration. The results of quinine administration appear more slowly. When more clinicians investigate its therapeutic potentialities there is a possibility that quinine will gain much favor and may even supplant iodine in this disease.

LABORATORY DATA ON QUININE

Kroszczynski and Modrakowsky (1), experimenting on tadpoles, found that the physiological action of quinine is opposed to that of thyroxin.

Bromberg and Gray (2) quote Hardikar (3) to substantiate their views to the effect that the theoretic reasons which have been adduced to explain the alleged beneficial action of quinine in thyrotoxic states are greatly disputed. In the same communication, however, these observers quote Mills (4) who, experimenting on rabbits, concludes as follows: "By the action of quinine on the animals, it was possible to influence principally the endogenous metabolism and observe the results of this on thyroid activity. As the results indicate, there occurs a diminished activity of the gland. Since quinine has no known action directly on the thyroid, it seems that the depressed protein metabolism must cause the decreased thyroid activity, probably by bringing about a diminished need for the secretion in the body and allowing its storage as colloid in the gland vessicles."

Sugata (5), confirming Mills' findings, found that quinine reduced the activity of the thyroid in rabbits and dogs. Sugata says: "In the quinine series, the iodine content of the thyroid increased remarkably and without exception. The increase of iodine in the quinine series was so great that there was no room for doubt of the effect of quinine on the iodine accumulation in the thyroid." Morphological changes were found by Sugata to parallel the iodine changes.

Although their findings were negative with respect to guinea pigs, Bromberg and Gray (2) state: "Quinine appears to suppress compensatory hypertrophy of the thyroid gland in the rabbit. . . . The effect of quinine on the compensatory hypertrophy of the rabbit thyroid gland resembles closely the effect of iodine noted by Marine in the same animal."

THE QUININE TEST FOR HYPERTHYROIDISM

In 1920, finding a singular insusceptibility to cinchonism in a series of sufferers from thyroid hypersecretion (especially in association with Graves' syndrome), I formulated the quinine test for hyperthyroidism (6), the technic of which is as follows:

> The patient is given a dozen capsules, each containing 10 grains (0.65 gm.) of quinine sulphate, with instructions to take a capsule four times a day. After 20 or 30 grains (1.3 or 1.9 gm.) have been taken by persons in whom thyroid function is normal or deficient, symptoms of cinchonism develop. A sense of fullness in the head, impaired hearing with tinnitus, occasional dizziness and headache, and less frequently, gastric and bladder discomfort are experienced. If, however, the patient is suffering with hyperthyroidism, the daily administration of 30 grains of quinine may be continued with impunity for weeks or months, often with distinct improvement in the clinical picture.

At this writing (October, 1931), we have applied the test to approximately 2000 patients with hyperthyroidism, chiefly those with Graves' disease, with an error of approximately 5 per cent. Included in the percentage of error was an occasional instance of quinine sensitivity or idiosyncrasy amounting to approximately one per cent.

The quinine test as a diagnostic procedure appears to present several advantages over other laboratory procedures in the examination of these patients, among which are its simplicity, its dependability, and the fact that its results are not influenced by emotionalism, transient nervousness or errors in technic. The most important advantage is that the test requires no preliminary period of rest or starvation.

Among those who find this test useful are Pfahler (7), and Parisot and Richard (8). Bromberg and Gray (2) also found their small series of cases relatively immune to cinchonism.

QUININE IN TREATMENT

As far back as 1885, Forschheimer (9) demonstrated the efficacy of quinine hydrobromide in a large series of sufferers from exophthalmic goiter. Subsequently, many others were able to confirm his findings.

Jackson and Mead (10), for instance, regard quinine hydrobromide as a very important asset in treatment. They rightly insist, however, that irrespective of the great value of this drug treatment, results may not be forthcoming before several weeks have elapsed, and patience must be exercised, for treatment may be requird for a year longer. Also, they emphasize the importance of not relying merely upon a drug for the management of exophthalmic goiter. To quote: . . . "We cannot advocate sending early cases to the surgeon. The results of medical treatment are too favorable, from 70 to 80 per cent of the cases being cured by it."

Clendening (11), too, advocates quinine as the drug he uses most frequently in the routine treatment of intoxication from the thyroid gland.

Benhamou (12) reports the case of a woman of 45, to whom he administered quinidine for paroxysmal tachycardia. Prior to treatment with quinidine, she had had an old-standing goiter which suddenly increased in size with aggravation of the paroxysmal tachycardia. The result of the quinidine treatment was stabilization of the heart's action, with decrease in the size of the goiter which eventually disappeared.

Bromberg and Gray (2), under the caption, "Clinical Trial of Quinine," mention their observations on five previously untreated cases of exophthalmic goiter on the adult medical service of the Barnes Hospital. Apparently in an effort to check up my findings, they administered quinine sulphate in two gram doses (30 grains) daily (0.6 gm. t.i.d. p.c.) by mouth for from two to three weeks, without any resulting improvement in basal metabolic rate or in clinical manifestations. Their negative results were due, in my opinion, to the fact that their patients were under hospital attention awaiting thyroidectomy. Our patients were observed for much longer periods and were neither under hospital attention nor under apprehension of impending operation. They were under a broad regime of attention.

Not only was the period of quinine administration by Bromberg and Gray too brief, but the circumstances under which it was administered nullified any possible good that could be expected of the drug. This was true also with the small series of cases under observation by Means and Aub (13), whom Bromberg and Gray quote in their paper. These observers failed to heed my note of caution in the Archives of Internal Medicine (14), in which I stated: "It must not be construed, however, that quinine, whatever its virtues, is the main factor in the treatment of exophthalmic goiter. A mere drug cannot be depended on for the cure of this disease. Quinine, however, the basis of the Forschheimer treatment, may be regarded as a valuable constituent in the armamentarium of the experienced internist who has sufficient confidence in himself to treat successfully patients with exophthalmic goiter without resorting to an operation."

But Bromberg and Gray (2) admit that the increased tolerance to quinine which I emphasized was a constant finding in their short series of cases. Also, they found that in one patient operated on only after quinine sulphate preparation, "the histological picture of the thyroid gland showed focal hypoplasia and moderate increase of colloid such as is often noted in exophthalmic goiter patients who have received insufficient preoperative iodine." It is interesting to note that Kleinschmidt (15) finds the results of the administration of quinine hydrobromide, instead of iodine, as a preoperative and postoperative treatment, very useful. Judging from our own clinical observations following maximal quinine doses, it would appear that any deficiency in preoperative results from the administration of quinine is assignable to insufficiency of dosage. A minimum of 30 grains

of quinine sulphate a day administered over a period of at least four weeks, with the patient in bed and under a high caloric diet and proper psychotherapy is, in our experience, quite comparable to preoperative iodine administration, with the added advantages that quinine does not lead to an exacerbation of symptomatology after benefit from its use is evident.

My observations (6, 14, 16), published and unpublished, on the use of quinine in hyperthyroidism, especially when associated with Graves' syndrome, extend over a period of 21 years and embrace a series of more than 2000 patients to date. Approximately 95 per cent of these patients could take from 30 to 90 grains of quinine sulphate daily, not alone without evidences of cinchonism, but, in many instances with distinct benefit. In 60 per cent it was felt that credit could be given to quinine for very favorable progress in recession of general symptoms. From the evidence at hand it would appear that the physiological action of quinine favors either a curbing of excessive thyroid output, or a neutralization of excessive thyroxin in the blood, or both. Though quinine cannot be looked upon as the sole treatment of the disease, it certainly appears a useful asset in the management of these cases, whether basically this treatment be surgical, roentgenological or medical.

Our patients were observed from a purely medical aspect. It is generally conceded that the psychic factor plays a major rôle not alone in the etiology of Graves' disease, but also in symptomatology, and very much so in treatment. Hence in addition to quinine administration, psychotherapy, in which efforts were directed toward the maintenance of a state of peace and tranquillity, was a major concern in the treatment of our patients. Moreover, discoverable etiological factors as infectious foci in teeth, tonsils and elsewhere, were corrected insofar as was possible and at the proper time. A high caloric diet with a minimum of flesh protein was established. In the realization that an enforced stay in bed imposed upon one whose physical and mental faculties are highly quickened might do more harm than good, only the small percentage of those patients who presented cardiac lesions were placed at absolute rest for a short time. The remainder were permitted a moderate amount of out-door life and prescribed exercise. Approximately 10 per cent of these patients were under our observation at our Goiter Sanitarium in the country; the remainder were under home attention. None of these patients was kept in the hospital, for experience has taught us that unless thyroidectomy is contemplated, the average subject of Graves' disease does poorly under hospital environment.

While it may be stated that the credit for favorable progress may be assigned to therapeutic factors other than quinine, we satisfied ourselves on this point in 1929 by making a comparison in two series of cases, both treated exactly alike, with the exception that in one the quinine was omitted. One hundred patients suffering with exophthalmic goiter were selected for this observation. The average age was 30 years, the average basal metabolic rate plus 38 per cent, and the average pulse rate was 118.

Seventy-two patients were females and 28 males. Dividing this series numerically into two groups and as evenly as possible with respect to age, sex, and severity of the disease, one group was treated along broad medical lines without the administration of quinine. To the other group, treated similarly, quinine was administered in dosage varying from gr. x to gr. xx t.i.d. At the termination of eight weeks those without quinine had progressed to the extent of a reduction of 18 points in basal metabolic rate, an average reduction of 27 points in pulse rate, and an average increase in weight of 12½ pounds. The patients receiving quinine progressed more rapidly, presenting an average reduction of 29 points in the basal metabolism, 38 points in pulse rate and an average increase of 18 pounds in weight. At the termination of the eight weeks, approximately 30 per cent of patients in the latter group had reached normal metabolic rate, pulse rate and weight along with perfect sense of well-being, and were eager to resume their usual duties.

COMPARATIVE VALUE OF QUININE AND IODINE

Quinine has no known influence on the prevention of goiter. Also, there is no evidence to indicate that quinine has any curative effect upon simple or nonhyperplastic goiter. Sufferers from nontoxic goiter can take no more quinine than can normal individuals. Indeed, I have recently found that subjects with thyroid hypoactivity can tolerate less quinine than those presenting a normal metabolic rate. Quinine is useful solely in combatting the symptoms of the hyperthyroid state particularly when this is a constituent of Graves' syndrome.

The value of iodine in the prevention of simple endemic goiter is almost universally recognized. While iodine is of doubtful use as a cure in already established goiter, in a percentage of cases without goiter iodine may stimulate the sluggish thyroid into better function. However, the administration of iodine in the presence of goiter may result in marked increase in size of the mass through an increased accumulation of colloid.

The administration of quinine does not engender the marked increase in the size of the thyroid gland. Any enlargement of the organ following quinine medication is transient, inconsequential and is followed in course of time by obvious reduction in size of the hyperplastic thyroid.

While incautious iodine administration may flare a simple goiter into toxicity, such is not the case with quinine administration. In the absence of sensitivity, the most that can occur from careless quinine medication is cinchonism, without tangible involvement of the thyroid gland.

In the average case of hyperthyroidism, especially with Graves' syndrome, the beneficial effects of iodine administration are more prompt and even spectacular as compared with results of quinine administration. However, iodine results are transient in the usual patient, and followed within approximately three weeks by cancellation of the benefit and soon by obvious symptoms of increased intoxication to which the term iodine-Basedow may be applied.

Not so with quinine administration. While the results of the exhibition of quinine are more tardy, making their appearance within three or four weeks or longer, the effects are cumulative. In association with other appropriate measures quinine medication may result in recovery within several months in the average patient.

QUININE COMBINED WITH IODINE

In a series of 25 cases of exophthalmic goiter a combination of quinine gr.x and iodine (in the form of Sajodin gr.i) was given t.i.d. and the results were compared with a similar series in which quinine was the only drug given, and with still another series in which the only drug employed was iodine in the form of Sajodin gr.i, t.i.d. It was evident that for periods of time the two drugs are synergistic one with the other. In other words, the complementary effects of iodine with quinine expedited and intensified the beneficial results. At the termination of four weeks the iodine was discontinued, but there was no recurrence of the symptoms observed prior to medication, nor was there observed the classic secondary rise of symptoms so commonly seen at the termination of approximately three weeks of iodine administration. I had long suspected that quinine is a deterrent to the exacerbation in symptomatology following iodine administration, and this series of observation apparently confirmed that view. We felt justified in concluding that in patients receiving both quinine and iodine favorable progress within four weeks was approximately 25 per cent more marked than in patients receiving quinine or iodine alone.

Also, in combination, quinine and iodine produce results at a much earlier date than when either is given alone. The combination may be given for a period of two weeks, when the iodine may be discontinued for a week or 10 days, then readministered for a like period.

WHEN TO DISCONTINUE QUININE

In order to obtain the best results, the quinine must not be discontinued (although the dosage may be reduced), until the high metabolic rate, heart rate, and other symptoms of the disease have disappeared, when it will be found that the patient can take scarcely more quinine than can a normal person. In other words, in order that the most satisfactory results be obtained, the quinine must be continued until evidences of cinchonism appear. In our patients it was observed that the relative immunity to cinchonism obtains only during the time the individual is suffering from the disease, the amount of quinine satisfactorily tolerated by the patient running fairly parallel with the height of the basal metabolic rate. When, having been capable of taking 30 or more grains of quinine sulphate with impunity for weeks or months, the patient complains of buzzing in the ears and roaring in the head, it will be found that the heart and metabolic rates and sense of well-being have become quite normal.

At this point it is well to continue giving quinine in doses tolerated without cinchonism, which in the average individual may vary from 3 to

10 grains a day. This dosage is suggested for three to six months, then permanently discontinued.

Of course, discharged subjects of exophthalmic goiter should be followed up for a period of from three to ten years, not by mail, but by a personal study every three to six months. It is only in this way that irreproachable statistical records can be had and a proper evaluation can be made of the virtues of a given mode of treatment.

SUMMARY AND CONCLUSIONS

1. Subjects of exophthalmic goiter are relatively insusceptible to cinchonism and can take quinine in doses of 30 to 90 grains daily with impunity and often with benefit.

2. This is the basis of the quinine test for hyperthyroidism especially when associated with Graves' disease, and is again recommended as a safe, simple and dependable diagnostic procedure.

3. The effects of quinine in exophthalmic goiter resemble, in many respects, those of iodine. Following its use there occurs in the average case an amelioration of the symptomatology of the syndrome.

4. Quinine in large doses is a valuable asset in the armamentarium of the internist who has sufficient experience with subjects of Graves' disease to realize the complex needs of these patients. It must be emphasized that quinine is not the mainstay, but is a valuable asset in the broad regime of therapeusis which must include attention to discoverable etiological factors, diet, psychotherapy and proper environment.

5. Quinine differs from iodine administration in exophthalmic goiter in the following respects: (a) quinine can be given for an indefinite period of time without danger of flaring up of symptoms; (b) it does not produce the marked increase in size of the thyroid that often occurs after iodine administration; (c) while the beneficial effects of quinine are slower in appearing than those of iodine, the results are continuous and cumulative.

6. Quinine and iodine may complement each other in treatment. Also, quinine in proper dosage given in combination with iodine in small doses appears in the average case to serve as a deterrent to the classic rise in symptoms following prolonged iodine administration.

7. When recovery is reached the singular tolerance to large doses of quinine gives way to normal susceptibility to cinchonism.

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THE SYNDROME OF ADRENAL HEMORRHAGE IN THE NEW-BORN*

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In this communication we shall endeavor to show that an intra vitam diagnosis of adrenal hemorrhage in the new-born can be made upon the presence of a definite clinical syndrome. This contention is based upon personal findings corroborated by the observations of others.

The numerous case reports in the literature indicate that this is not a rare condition. The earlier writers like Mattei (1), Lesser (2), Gakowski (3), Dorner (4), Still (5) and Spencer (6) were able to collect 70 cases out of about 4,500 autopsies, but their reports were little more than descriptions of the post mortem findings. The reviews of Arnaud (7), Magnus (8), Hamill (9) and Friderichsen (10), while they do not contain a single instance where the diagnosis of adrenal hemorrhage was suggested during life, are of value as some of the collected data will permit clinical analysis. Unfortunately a large proportion of their cases also were of still-born subjects and obviously of no aid in our present study. Hamill (9) bases his report on 80 cases, only 20 of which offer any clinical information. Some of Hamill's and most of Magnus' are included in Friderichsen's (10) able resumé of 29 cases. Arnaud (7) includes adults in his review of 79 instances of adrenal hemorrhage but over half of them are without clinical description. Of the 26 new-born children and infants in his series, only eight were accompanied by some symptoms.

We have been able to collect 37 cases of adrenal hemorrhage in the new-born and 38 in older infants which offer some clinical information. To these we contribute the following six additional instances in the new-born, five of which were diagnosed during life. These 81 cases form the basis of this present study.

REPORT OF CASES

Case 1. Service of Dr. M. B. Gordon at United Israel Zion Hospital.

The mother, 37 years of age, had had 4 full-term pregnancies and 3 miscarriages. There was no history of any blood dyscrasia in the family. An antenatal Wassermann test on the mother was negative. The child was delivered after 5½ hours of labor without any difficulty on May 9th, 1929, at 11:15 A. M., weighing 10 pounds and 7 ounces.

Nothing unusual was noted until the evening of the 12th when a slight cyanosis of the finger tips was observed. The temperature was 101.8°F. and respirations, 80 at 2 A. M. The respirations were irregular and rapid, cyanosis was more pronounced and the temperature was 102°. By 6:40 A. M. the breathing had assumed the Biot type with a rate of 96 to the minute. At this time some scattered mottled areas of purplish discoloration were noted on the skin of the upper left arm.

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At 9:30 A. M. complete examination revealed the following:

A well developed and nourished female infant who was markedly dyspneic with dilatation of the alae nasi, showing respiratory grunt and marked heaving and pulling of the chest wall. The eyes were injected. The color was dusky with a cyanosis more marked in the finger tips and lips. The skin showed a small area of purplish colored macular eruption on the upper left arm. Examination of the chest did not disclose any signs of pulmonic involvement on either physical or fluoroscopic investigation. The heart sounds were rapid, of fair myocardial tone and without any murmurs. Abdominal examination showed a smooth, freely movable, rounded mass about the size of a small egg in each kidney region, while on the right side there was a more doughy feeling underneath the skin. Neurological signs were absent except for a marked hyperacusis. During the course of the examination, a rusty, loose stool, mucoid in character and small in amount, was passed. Clinical diagnosis of bilateral adrenal apoplexy was made.

Laboratory data: Blood drawn from the toe was quite dark in color and showed a bleeding time of 13 minutes and coagulation time of 7 minutes. During the course of a routine study of the blood sugar in the new-born, Dr. S. Pennell found the following values in this child:

May 10th at 22 hours of age, blood sugar content: 50-59 mgm. per 100cc.
May 11th at 46 hours of age, blood sugar content: 44-46 mgm. per 100cc.
May 12th at 94 hours of age (6 hours prior to death): 10-10 mgm. per 100cc.

Post mortem findings: Upon opening the peritoneal cavity about three ounces of a serosanguinous fluid was found. There were two or three ounces of a clear yellow fluid in the pericardium. Both adrenals were markedly enlarged to about two-thirds the size of the kidneys; they were red in color and when punctured, a dark red fluid poured out. The capsules were intact. Small, dark red colored areas were present in the small intestines, especially in the ileum.

Anatomical diagnosis: Bilateral adrenal hemorrhage; hemoperitoneum and pericardial effusion were noted.

Through the courtesy of Dr. Carl H. Laws and the Pediatric Staff of Long Island College Hospital, we are enabled to include the following four cases which are reported for the first time.

Case 2. (Dr. Lambert Krahulik)

Baby R. was delivered by forceps on November 9, 1930. Examination shortly after birth gave the following positive findings: Cyanosis; rapid, shallow irregular respirations; weak and rapid pulse and normal temperature. The child died in two days from what was diagnosed as intracranial hemorrhage.

On autopsy it was found that the tentorium cerebelli presented a ragged 2 cm. tear on the left side in the superficial layers. There were no gross signs of hemorrhage in the brain or of free blood in the posterior fossa. The right kidney presented marked hemorrhage in both cortex and medulla. Both adrenals likewise showed pronounced hemorrhage in the cortex and medulla.

Case 3. (Dr. Lambert Krahulik)

Baby A., born by spontaneous delivery, showed no untoward symptoms until the 5th day when a slight umbilical infection and jaundice were noted. On the 9th day of life, general clonic convulsions appeared at frequent intervals. Vomiting occurred several times that day. Respirations were rapid, irregular and shallow without signs of any pulmonic involvement. The temperature was normal. The abdomen was so markedly distended that a detailed examination was impossible. The reflexes were exaggerated, the pupils dilated but fontanelle was not bulging. A lumbar puncture was performed on the assumption of an intracranial hemorrhage being present but the results were practically negative and the diagnosis was changed to that of possible adrenal hemorrhage.

The convulsions continued at frequent intervals for the next few days. On the 14th day after delivery the temperature rose to 101°F. the respirations were still rapid and the abdomen was still distended. There was a marked pallor with a corresponding drop in hemoglobin from 70 to 50 per cent and a diminution in red blood cells from four and one-half to two and one-half millions. The child was stuporous. The umbilical infection was cured. On the 30th day of life a salmon colored maculo-papular rash appeared over the entire body with the

exception of the soles and palms. The color seemed to change to a bronzed appearance in a few days. Broncho-pneumonia was observed on the 38th day and death occurred on the 40th day of life.

Laboratory data: Blood examination on the 9th day showed: red blood cells, 4,500,000; white blood cells, 13,200; polymorphonuclears, 68; lymphocytes, 23; hemoglobin, 70 per cent; coagulation time, 3 minutes; bleeding time, 2 minutes. The Wassermann reaction was negative.

Treatment consisted of intravenous transfusions and intramuscular injections of blood.

Autopsy findings: The abdomen was distended but no fluid was obtained on opening the peritoneal cavity. A cyst, 4 cm. in diameter, was found attached to the pole of the left kidney and filled with coagulated blood. The wall consisted of the fibrous capsule in parts of which was some adrenal tissue. There was a similar appearing cyst, 6 cm. in diameter, above and attached to the right kidney, which was filled with a greenish fluid consisting of pus and blood.

Case 4. (Dr. Lambert Krahulik)

Baby M. was delivered spontaneously on Dec. 1, 1930, and did not show anything abnormal until 7 hours later when it was noted that the respirations were rapid and accompanied by an almost shrill cry. There was very little cyanosis, the skin was slightly jaundiced, the temperature was normal as were the lungs. The abdomen was distended and gave a feeling of tenseness on the right side. Adrenal hemorrhage of the right side was suspected and 300 cc. of blood was administered intravenously. The coagulation and bleeding time were normal. The hemoglobin was 70 per cent.

By the next day the child had become drowsy, sleeping most of the time, but when awakened it cried lustily. The respirations continued rapid and irregular. Abdominal examination revealed a small mass with a sense of fulness. Jaundice was more marked. Blood sugar determination showed a value of 89 mgm. per 100 cc. Intramuscular injection of 50 cc. of the infant's blood serum into the lymph sac of a frog and into the eye did not produce any dilation, showing loss of adrenin. Hypodermoclysis and further injections of blood were given. The general condition improved, the abdomen became softer, the mass subsided and the child was discharged in a fair condition on Dec. 15th. The temperature ranged from 98 to 100 degrees but the respirations continued rapid until a few days prior to discharge.

Case 5. (Dr. Chas. Weymuller)

Baby D. was full term, normal delivery. Examination on the second day of life showed prostration with cyanosis, dyspnea and rapid respirations. The abdomen was rather full but did not show any masses. A diagnosis of possible intracranial hemorrhage was made and a lumbar puncture performed with negative findings. The temperature was 99°. By the next evening the child was decidedly worse, the respirations had increased in rate and were much more labored; the temperature had risen to 102° and a definite mass could be made out on the right side of the abdomen. Bleeding and coagulation time were normal. The Wassermann reaction was negative. The diagnosis was changed to adrenal hemorrhage. Transfusion of 100 cc. of blood was administered. The patient responded and gradually improved, being discharged in two weeks, at which time the mass was markedly reduced in size.

Case 6. (Dr. J. Rosenblum at Coney Island Hospital, Service of Dr. Pendleton)

Baby T. was born on March 12th, 1930. in a partially asphxiated condition but responded to artificial resuscitation in the form of mouth to mouth insufflation, pressure on ribs and alternate immersion in hot and cold water. Cyanosis persisted for two hours. On the following day hemorrhages were noted in the sclerae. The temperature rose steadily from then on, reaching 105° on the third day of life. Complete examination on that day showed the following: The infant appeared critically ill; the face was yellowish with a circumoral cyanosis. The cry was weak; the sclerae showed hemorrhages; the temperature was 105°; respirations were rapid and shallow, varying in rate from 120 to 170 per minute; the breath sounds were normal throughout the chest and the abdomen was slightly distended. In the left flank of the abdomen a freely movable oval tumor mass about the size of an egg was palpable. A diagnosis of adrenal hemorrhage

was made. A small hemorrhagic area was noted under the left scapular region the next day. The temperature ranged from 105° to 108° then gradually subsided, reaching normal by March 22nd, 7 days after the onset of the condition and 10 days after birth. The child was discharged on March 21st in good condition, with normal temperature, respirations of 60 and a slightly reduced mass.

Treatment consisted of intramuscular injections of blood.

Laboratory data: March 16th (one day after onset), examinations disclosed red blood cells, 5,130,000; white blood cells, 13,000; polymorphonuclears, 60 per cent; small lymphocytes, 32 per cent; monocytes, 8 per cent; Hb. (Sahli), 94 per cent; bleeding time, 1 min.; coagulation time, 5½ min. The blood urea nitrogen was 30 mgm.; creatinine, 2.8 mgm.; uric acid, 6.6 mgm.; glocose, 63 mgm. in 100 cc. of blood. On March 20th, the urea nitrogen was 16.7 mgm.; creatinine, 1.4 mgm. The Wassermann reaction was negative.

PATHOGENESIS

The adrenal gland is probably the most vascular organ during the neonatal period and is extremely friable. Immediately after birth an involution process takes place in which the reticular and trabecular layers are destroyed and then replaced by a highly vascularized fibrillar connective tissue. It is obvious that such a degree of hyperemia and congestion is conducive to minute bleeding which, under certain conditions, may become extensive.

It is not our intention to discuss at length the pathogenesis of adrenal hemorrhage beyond stating that the factors responsible for the occurrence of this lesion may be grouped into the following three general classes:

(1) Those related to *labor* (trauma during birth, asphyxia neonatorum, trauma due to artificial resuscitation, eclampsia in mother). (2) *Local conditions* (physiological involution of adrenal cortex, stasis due to compression of vena cava between liver and vertebral column, thrombosis of suprarenal vein). (3) *General conditions* (hemorrhagic diathesis, acute infections, syphilis).

The lesions vary considerably in extent and may be classified as follows (Goldzieher, 1): (1) *Small hemorrhages* which infiltrate the stroma and fill the lymph and pericellular spaces without any apparent destruction of tissue elements; (2) *Diffuse hemorrhagic infarction* of the entire adrenal without destruction of tissue; (3) *Destructive hemorrhages* which begin in the innermost cortical layer and transform the gland into a hemorrhagic cyst of variable size; (4) *Massive hemorrhage,* the severest form, in which the organ is converted into a sac which may exceed the original size of the organ. Rupture into the peritoneal cavity or retroperitoneal connective tissue may follow due to distension and rupture of the capsule. Small hemorrhages are common and may heal rapidly, leaving only a slight pigmented scar. Large hematomas may be absorbed and heal with extensive scarring or calcification. Extensive hemorrhages, particularly of the destructive type are most frequently bilateral.

CLASSIFICATION

The confusion as to the symptomatology of adrenal hemorrhage is portrayed in the various classifications which have been advanced by several

authors. Most of these have been based upon the time of occurrence. Hamill (9) considers that there are three types in the still-born, depending upon the relationship between the time of occurrence and delivery. We are not concerned with this grouping. Still (5) states that there are three classes in the new-born: (1) Those in which death occurs in a few hours or days after birth; (2) Those in which death occurs after the sixth day as a complication of some disease, usually of the respiratory tract; (3) Those which occur incidental to some infection. The most practical classification is that of Comby (12), who differentiates between the adrenal hemorrhage in the new-born, older children and adults. The importance of this grouping, from a physiological viewpoint, will be discussed later.

Classification according to clinical manifestations is best exemplified in Arnaud's (7) original description in which he suggested the following: (1) Those with insufficient clinical symptoms; (2) Extensive hemorrhage, capable of causing symptoms or a palpable tumor; (3) Intraperitoneal hemorrhage; (4) Symptoms of adrenal insufficiency; (5) Nervous symptoms. Unfortunately, 44 of the 79 cases upon which this classification was based fell into the first group of insufficient clinical manifestations. There were no children or new-born in the group with symptoms of adrenal insufficiency. Lavenson (13) and Dudgeon (14) advanced modifications of the above classification and emphasized the types with an acute onset or sudden death.

The value of any classification lies in its clarity and practicability. Comby's grouping according to age correctly implies the existence of a difference in symptomatology in the various ages but it is of little diagnostic aid, *per se*. Arnaud's classification, which was advanced 30 years ago, is now antiquated because of the advances made in endocrinology. This applies particularly to his conception of what constitutes acute adrenal insufficiency.

Upon the basis of recent experimental evidence, an analysis of the 81 cases in the present study justifies the following *classification* of the symptoms of adrenal hemorrhage in the new-born:

1. *Symptoms of acute adrenal insufficiency:*

(a) *Endocrine:* Rapid respiration, high temperature, rash (purpura or petechiae), metabolic changes, convulsions and cyanosis; (b) *Associated symptoms:* Gastro-intestinal disturbances such as vomiting, diarrhea and abdominal pain; nervous conditions such as coma, convulsions and twitchings.

2. *Symptoms of adrenal hemorrhage:* (a) *General:* Shock; collapse; weak and irregular, small pulse; cold extremities; air hunger; increasing pallor; (b) *Local:* The abdomen is generally distended and gives a boggy sensation; abdominal pain; palpable tumor in one or both kidney regions; peritoneal symptoms with intraperitoneal hemorrhage.

SYMPTOMS

While the severity and duration of labor play an important part in the production of adrenal hemorrhage, a large percentage of the cases have occurred in normal deliveries. Asphyxia neonatorum is not present, as a rule. Within a few hours or days after birth it is noted that the infant presents a clinical picture suggestive of pneumonia with rapid respiration and an increasing temperature but without any physical signs of pulmonary involvement. In fact, a number of the cases have been erroneously diagnosed and treated as pneumonia. This resemblance is so marked that we suggest that the descriptive term of "pseudo-pneumonia of the new-born" be applied to this part of the syndrome. The infant generally refuses nourishment, may be apathetic, cyanotic and show a petechial rash over portions of the body or extremities. Examination of the abdomen at this time may reveal a unilateral or bilateral mass in the renal region; the abdomen itself is distended and boggy in most instances. Vomiting, convulsions, twitchings, jaundice and diarrhea may also be present.

In place of this picture, we may have one in which the onset is very acute and the dominant signs are those of shock, collapse, and death within a short period of 24 to 48 hours.

In older infants and children the onset may be ushered in by acute abdominal pain which is severe enough to arouse the child with a sharp cry from its sleep. The subsequent course is that of the "pseudo-pneumonia" with its rapid respiration and hyperpyrexia, rash, vomiting and convulsions. In a number of cases observed in adults, a somewhat similar picture has been noted, although the pseudo-pneumonic character was by far less striking [Cramer (5), Brasser (16), Brodnitz (17), Freudemann (18), Goldzieher (19), Hektoen (20), Severn (21)].

The above pictures may be reconstructed from the individual symptoms gleaned from the older literature and from the fairly complete clinical description of more recent reports. The predominating symptoms in the 81 cases under discussion, in the order of their frequency, are: high temperature, skin rash, rapid or irregular respiration, cyanosis, convulsions or twitching, vomiting, collapse, abdominal tumor, jaundice and metabolic changes.

HIGH TEMPERATURE

Temperature is mentioned in only 21 new-born and 29 infants. It was above 102° in 12 of the former and in 25 of the latter, totalling 37 instances of hyperpyrexia in the 81 cases discussed. Physiological reasons for its greater preponderance in the older children will be considered later in the paper. In four cases there was an accompanying acute infection which may have been responsible for the fever. Subnormal temperature was found at most in only six instances. It was definitely mentioned in four cases and may be assumed to have been present in two instances of collapse in which the temperature was not recorded. The comparative fre-

quency of high and low temperatures in this series establishes hyperpyrexia as an outstanding symptom and excludes subnormal temperature from the usual syndrome.

RASH

The appearance of a rash is mentioned in 35 of the reviewed cases. There is a certain discrepancy between the various authors as to frequency. Hamill (9) noted only one instance in his large series, while Friederichsen (10) found that it ranks with cyanosis as the most important symptom. Rabinowitz (22) made his *intra vitam* diagnosis practically on the basis of the characteristic petechial rash. This divergence of opinion seems to find its explanation in the difference in age of the patients. Hamill's series included mostly still-born and new-born subjects, while Friedrichsen's series and Rabinowitz's report dealt with older infants and children. In our series we also find that a rash was noted more frequently in the older patients, only 11 occurring in the new-born, 15 during the first year of life and nine in older children. In none of the eight cases in the adult with which we are acquainted, has a rash or petechiae been noted.

The type of rash is usually purpuric or petechial in character. Hemorrhages under the skin have been observed by a few. Cutaneous hemorrhages and bleeding from the mucous membranes of the intestinal or other tracts may also occur. Gordon's patient passed a rusty colored stool and post-mortem examination revealed small areas of patchy dark red color in the small intestines, especially in the ileum. Goldzieher and Greenwald (23) report vaginal bleeding and hemorrhagic areas in the selera and on the hard palate. Roessle (24) noted a patchy pigmentation of the palate in one patient. Rosenblum noted hemorrhages in both selerae.

According to Little (25), the relationship of purpura to adrenal hemorrhage is similar to that of pigmentation to Addison's disease. The bronzing of the skin in the latter is rarely mentioned in cases of hemorrhage, being noted, according to Arnaud (7), by Greenhow, Mattei, Addison, Garrington and Goolden. The appearance of pigmentation is a symptom of chronic or, at least, subacute adrenal insufficiency and is not to be expected in an acute condition which, as a rule, leads either to death within a few days or to complete recovery.

RAPID RESPIRATION

Increased respiration rate, reaching 120 in some instances, dyspnea, Cheyne-Stokes respiration or irregular breathing is mentioned in 20 newborn and 14 older infants and children. Respiratory embarrassment occurred in conjunction with high temperature in 18 instances. In the adult it was observed by Brodnitz (17) and Goldzieher (19); the latter reports the case of a woman who developed the syndrome of pseudopneumonia after an abdominal operation.

The respiratory symptoms are much more frequent in the new-born than at any other age. The relationship of the respiratory symptoms

to age seems to us so important that we shall discuss it extensively later on.

CYANOSIS

Cyanosis is a fairly frequent symptom, being noted in 26 instances in the present series.

CONVULSIONS

Arnaud (7) found four instances in new-born subjects and infants and 15 in adults of what he terms the nervous group. This type is characterized by convulsions, coma and a "typhoid like" state with practically no other signs. In our series there were 13 instances in the new-born (including the four described by the latter author) and five in older infants where convulsions or twitchings formed part of the picture.

VOMITING

This is generally described as a prominent symptom but it occurred in only 16 instances. It is of little value, *per se*.

JAUNDICE

This is also of slight significance, especially in the new-born. It is probably not related to either the endocrine or the hemorrhagic element of adrenal hemorrhage, but forms part of the physiological picture of the new-born.

METABOLIC CHANGES

As far as we could ascertain there is no mention made of any metabolism studies prior to those of Gordon, Krahulik and Rosenblum. These observers noted a decrease in the level of blood sugar. Rosenblum also found an increase in nitrogenous metabolites. The metabolic changes will be considered in detail later.

COAGULATION AND BLEEDING TIME

These have been found to be within normal limits by the several authors who studied this phase of the subject.

HEMORRHAGE

The signs of adrenal hemorrhage are those of uncontrolled, concealed, internal bleeding—shock, collapse, cold extremities, weak and small pulse, air-hunger, increasing anemia and pallor. These were the predominating symptoms in 14 instances. To these may be added local abdominal signs such as distention, feeling of bogginess and, in extensive hemorrhage, a palpable tumor in one or both kidney regions. An abdominal mass was noted in eight of the cases diagnosed during life. Unless the abdominal condition is recognized, the picture of internal bleeding is erroneously considered as being due to intracranial hemorrhage or hemorrhagic disease of the new-born.

Rayer (26) was the first to suggest that the combination of signs of internal hemorrhage and presence of an abdominal tumor was sufficient

evidence upon which to make a diagnosis of adrenal hemorrhage in the new-born, in the absence of signs pointing to other organs. Where rupture has occurred through the adrenal capsule into the peritoneal cavity with a resultant hemoperitoneum, the differential diagnosis may be much more difficult. There are 11 instances of hemoperitoneum in the literature. In older infants and children the abdominal distress may be so acute as to suggest an acute surgical condition. Of the number of instances in which operation was performed upon this supposition, that of Corcoran and Strauss (27) was the only one in which the condition was recognized, proper treatment instituted (removal of the clot and ligation of the bleeding vessels), and recovery obtained.

The severity of the hemorrhagic manifestations depends upon the amount of bleeding. Not all cases terminate fatally as the hemorrhage may cease and the clot be absorbed. Signs of previous adrenal hemorrhage are frequently found at autopsy in patients who die at some subsequent time of other conditions. On the other hand, especially in bilateral involvement, the bleeding may be so severe as to cause death within a few hours or days. The case may be terminated before the production of insufficiency symptoms or the hemorrhagic picture may mask those of adrenal disturbance. Arnold's (28) four cases are excellent examples of the latter situation and will explain the absence of any endocrine symptoms.

PHYSIOLOGICAL CONSIDERATION OF ENDOCRINE SYMPTOMS

In analyzing the endocrine symptoms, disregarding those referable to hemorrhage, we shall discuss at this point changes in temperature, respiration and metabolism. Convulsions also possibly belong in this group.

Hyperpyrexia, which was observed in all our personal cases, was noted in 37 out of 59 cases in the new-born and children and in seven of eight cases in the adult. It seems that this symptom is directly related to functional disturbance of the adrenal gland. In this respect two different points must be considered. The adrenal medulla, according to Cramer (15), participates in the regulation of body temperature by stimulating the sympathetic nervous system and, particularly, the thyroid gland. Even more important is the function of the adrenal cortex which, according to Marine and Bauman (29) and Scott (30), is that of checking the heat-producing activity of the thyroid. The experiments of these authors demonstrated that the removal or destruction of a sufficiently large amount of cortical tissue produces an increase in temperature, provided the function of the thyroid is unimpaired. Previous thyroidectomy prevents such hyperpyrexia, showing that the influence of adrenal cortex upon body temperature is only an indirect one.

In view of this indirect relationship between the adrenal cortex and heat regulation it is not surprising to note a normal or even subnormal temperature in some of the cases of adrenal hemorrhage. In the light of

experimental evidence we cannot expect a change of temperature if a sufficient amount of cortical tissue has been left unimpaired. It must also be taken into consideration that some other endocrine correlations may compensate for the cortical insufficiency, at least so far as regulation of temperature is concerned.

Disturbances of the normal rate of *respiration* are also definitely referable to cortical insufficiency. Bornstein (31) deserves the credit for having drawn attention to the rapid respiration and subsequent hyperventilation of the lungs which occurs in dogs after bilateral adrenalectomy. His observations were corroborated by Golyakowski (3), Aub and coworkers (32), Reiss (50) and others. Marine and Bauman (29) found that those animals which lived indefinitely after adrenalectomy with no change in respiratory exchange had active accessory suprarenal tissue. The increase in the respiratory rate after adrenalectomy is followed eventually by a fall to, or below, normal, assuming the low, labored type in the terminal stage (Trendelenburg, 33).

That the changes in respiration are actually due to a lack of cortical hormone was shown experimentally by Kuehl (34), Vincent (35), and Kisch (36) in adrenalectomized animals, in which administration of cortical extracts restored the respiratory rate to normal. Goldzieher (23) succeeded in demonstrating this phenomenon in a patient with adrenal hemorrhage by reducing the respiratory rate from over 50 a minute to 31 by intravenous injection of Interrenin. Recently, Sazaki (37) showed that O_2 dissociation in the blood decreases after bilateral adrenalectomy and is restored to normal by administration of cortical hormone.

In view of these data, it seems surprising that the respiratory phenomenon is not observed in every case of adrenal hemorrhage. Pathological respiration is mentioned only in 20 new-born and 14 children among the entire series and occurred in the adult in only two of the eight cases cited. In other words, this symptom seems to be less frequent than hyperpyrexia and its frequency gradually decreases with increasing age of the patient. It is our opinion, however, that the symptom of rapid respiration is actually much more common in the new-born; we have noted it in all of the eight cases coming under our observation. It is probable that other observers did not pay much attention to the symptom and did not record it. This explanation will not hold in older children or adults in whom changes of respiration are obviously much more striking than in the new-born. An explanation of the greater prevalence of the respiratory reaction in the new-born as compared to that in older children and adults may be obtained from the following anatomical and physiological considerations.

The adrenal gland at birth is of comparatively enormous size. It is about one-third the size of the kidney, whereas in the adult the difference between the two organs is about 1 to 30. The average weight of the adrenal in the new born is 4.7 grams in the male and 5 grams in the female. In the adult, while the body weight increases about 20 times, the weight of the

adrenals barely more than doubles to 10.2 grams in the male and 10.6 in the female.

Structural changes of the adrenal cortex set in immediately after birth. They include destruction of the central cortical layers and their gradual substitution by well vascularized fibrillar connective tissue. Only a small seam of the cortex, underneath the capsule, escapes destruction and even that layer gradually changes its structure in order to re-arrange itself into a glomerular and fascicular layer comparable to that of the adult adrenal. The development of the innermost reticular layer is completed later. These post-fetal changes of the adrenal cortex culminate at the end of the first year. At this time the glands weigh only 3.3 grams in the male and 4 grams in the female. The regeneration period begins with the second year but the final structure of the gland with its fully developed medullary tissue is attained only at the time of adolescence.

If we consider the excessive size of the adrenal cortex during fetal life and its sudden degeneration following birth, it is reasonable to assume such changes to be due to differences in the physiological conditions of the new-born and fetus. As these alterations occur at a time when the child does not yet partake of food, the only altered condition, to the best of our knowledge, is the onset of respiration and the sudden increase of O_2 tension in the blood. The degeneration of the cortical tissue seems to indicate that the new-born does not require the large amounts of cortical hormone necessary during fetal life to maintain tissue respiration at the much lower fetal O_2 tension. The superfluous cortical tissue is gotten rid of by the process of involution.

The behavior of the cortex in the new-born stresses the relationship between cortex and tissue respiration. Experimental evidence obtained in cyanide poisoning and beri-beri brings out the same fact: in both these conditions there is an interference with tissue respiration and a simultaneous marked hypertrophy of the adrenal cortex (Hess, 38). Messerle (39) explained this observation upon the assumption that the cortical hyperplasia is a compensatory process tending to produce more cortical hormone. Such an excess of hormone appears necessary to maintain the impaired tissue respiration. The constant call for increased hormone production eventually expresses itself in hyperplasia of the glandular tissue.

Such experimental evidence together with the observations on adrenalectomized animals seems to indicate that the cortical hormone plays an important role in the regulation of respiration, either by directly furthering the process of oxygen utilization in the tissues or by influencing the nervous centers of respiration. If this be true it is easy to understand why sudden destruction of cortical tissue will elicit respiratory embrassment. It is to be expected that these changes will be more striking and less easily readjusted by compensatory regulations in the new-born which is physiologically still accustomed to an overabundance of cortical hormone.

It seems to us that these considerations offer a plausible explanation for the different response in respiration between the new-born, older children and adults.

The third symptom directly referable to the adrenal insufficiency is the change in the *chemical constituents* of the *blood*. Gordon was the first to note a marked hypoglycemia of 50 mgm. per 100 cc. which occurred prior to the onset of any pronounced clinical manifestations and which continued to drop in value until 10 mgm. per 100 cc. was recorded six hours before death. Krahulik obtained a blood sugar value of 89 mgm. per 100 cc. at a time when respiration was rapid and irregular but temperature was normal. Rosenblum's patient gave a value of 69 mgm. per 100 cc. Hypoglycemia is a well-known symptom in Addison's disease. It should be expected to occur also in acute adrenal insufficiency such as that caused by hemorrhage. The relationship between adrenal function and carbohydrate metabolism as established by numerous experiments explains these clinical manifestations. Porges and Schwartz (40) noted that adrenalectomy in dogs and rats was followed by rapid disappearance of glycogen from the liver and a progressive fall in blood sugar. Similar hypoglycemia after adrenalectomy has been found by Bornstein and Holm (31), Barlow (41), Cori and Cori (42), Swingle (43), Estrada (44), and Wyman and Walker (45). Sectioning of the nerves of the adrenals, without removal of the glands, also results in hypoglycemia. [Lumley and Nice (46), Britton (47), Geiling and Calvery (48).] The result of such denervation experiments seems to prove that lack of medullary function is the main factor in the development of hypoglycemia. A similar mechanism probably is responsible for the hypoglycemia which has been observed in adrenal hemorrhage.

Rosenblum studied the nitrogen metabolites in the blood and obtained increased values for urea, creatinin and uric acid. This is quite in accord with the nitrogen retention as observed in adrenalectomized animals. Hartman (49), moreover, showed that administration of cortical extracts reduces the retention and eventually brings about normal blood nitrogen values. It seems therefore justifiable to expect that increased nitrogen figures should be present in cases of adrenal hemorrhage and although this contention was borne out so far only in a single case, it should be taken into consideration in the future as an additional diagnostic procedure.

Another symptom which may be connected with the insufficiency of the adrenals is the occurence of convulsions and twitching. They commonly appear in connection with hypoglycemia and also in cases of nitrogen retention. We cannot offer proof that convulsions in adrenal hemorrhage are actually of hypoglycemic or uremic origin but such probabilities should be given consideration.

In discussing the role of adrenal insufficiency in the symptomatology of adrenal hemorrhage we wish to emphasize the difference between this syndrome and Addison's disease. Apparently this difference is not sufficiently

clear to some of the authors of recent publications (*e.g.,* Peterman, 51). Adrenal hemorrhage in the new-born destroys a gland consisting of an excessive amount of cortical and comparatively insignificant quantity of medullary tissue. The function of the gland is adapted to the special necessities of port-partum life and differs from that in later childhood and adult life. The continuous development of the adrenals up to puberty together with similar changes in other endocrine glands apparently accounts for the co-ordination of their function which most probably does not exist to that extent at the time of birth. This conception seems to be borne out by the difference in symptoms of adrenal hemorrhage in the adult. Moreover, Addison's disease is the result of a slowly progressing, destructive process with adjustments of metabolism and tissue respiration to the changing conditions, in contradistinction to the sudden destruction of the gland in the subject under discussion.

DIAGNOSIS

The consensus of opinion in the literature seems to be that the diagnosis of adrenal hemorrhage during life is very difficult. Some even venture to state that it is practically impossible, particularly in the new-born. Rabinowitz (22) in 1923 recognized the condition *intra vitam* in an infant of 17 months of age mainly on the basis of the purpura and on the similarity of the history and clinical picture to that observed in a previous case which had been diagnosed as pneumonia but which on autopsy revealed adrenal hemorrhage. Corcoran and Strauss (27) operated on a new-born infant for what was supposed to be a splenic tumor and found, instead, a hematoma of the adrenal. Goldzieher (23) was the first to diagnose adrenal hemorrhage in the new-born on the strength of the endocrine syndrome discussed in this paper. The infant presented a typical picture of "pseudo-pneumonia of the new-born" with high temperature and rapid respirations and cyanosis. Diagnosis was confirmed on autopsy. Arnold recently diagnosed the condition of the new-born during life on the basis of signs of internal hemorrhage and the presence of a palpable abdominal tumor. Altogether, *intra vitam* diagnoses in the new-born have been made in 11 instances in the last decade by the following: Goldzieher (23), Greenwald (23), Corcoran and Strauss (27), Arnold (28), Gordon, Krahulik, Weymuller and Rosenblum. The cases of the latter four are reported here for the first time. Diagnosis was confirmed at autopsy in five and made at operation in one. Recovery was obtained in six.

Of the four sets of symptoms discussed under "symptomatology" (acute adrenal insufficiency, associated endocrine manifestations, general and local signs of adrenal hemorrhage), three are of diagnostic import and may serve as criteria:

(1) Symptoms of acute adrenal insufficiency: The infant presents the appearance of "pseudo-pneumonia of the new born" with high temperature and rapid respirations which are not accompanied by any signs of

pulmonic involvement as elicited by physical or roentgenographical examination. In addition there are purpura or petechiae, convulsions and hypoglycemia. This type is apt to be confused with true pneumonia and entered as such on the hospital records unless corrected by post-mortem examination.

(2) General signs of internal hemorrhage: These do not differ from those present in any case of internal hemorrhage and may be so pronounced as to mask the endocrine symptoms.

(3) Abdominal tumor in the renal region and signs of abdominal distress: The presence of an abdominal tumor with signs of internal hemorrhage or with the development of a sudden high temperature and rapid respiratory rate is suggestive evidence of an adrenal hemorrhage in the new born.

TREATMENT

The fundamental principles upon which treatment must be based are the combatting of three symptoms: internal hemorrhage, adrenal insufficiency and hypoglycemia with or without convulsions.

In spite of the general opinion voiced in the literature that adrenal hemorrhage is not amenable to treatment, the report of several recoveries of what are undoubtedly instances of this condition should call for a more encouraging attitude. There is no doubt that there have been many subjects who recovered spontaneously, as indicated by signs of previous hemorrhage in patients who came to autopsy for other reasons at a subsequent time.

Internal hemorrhage should be treated by intravenous transfusion of blood. Arnold, Krahulik, Weymuller and Rosenblum made use of this method.

The symptoms of insufficiency are probably not as amenable to treatment. The ideal procedure is the injection of a potent cortical hormone extract. A beneficial effect should be manifested by a drop in temperature and a decrease in the respiratory rate. The only case in which this was tried was in that of Goldzieher and Greenwald (23) in 1927 in which Goldzieher's interrenin (52) was injected. The observers noted a drop in the respiratory rate following each administration of the extract. They have experimental evidence in favor of this procedure in the results obtained by Keuhl (34), Kisch (36) and Vincent (35). The beneficial results obtained with blood transfusion may in part be due to the cortical hormone content.

Hypoglycemia is probably present in most of the cases of adrenal hemorrhage especially in those accompanied by convulsions. Intravenous or hypodermic injections of 10 per cent glucose should be given for this condition once or twice a day until improvement is noted. On the basis of the results obtained in seven instances, Zwemer (53) considers that the administration of 5 per cent glucose solution in sufficient quantities will prolong the life of an epinephrectomized cat for an average of 200 hours. Swingle

(43) suggests that death in adrenalectomized animals is due to either hypoglycemia or acidosis. The former may be combated but the latter is not as amenable to treatment as the animals die because of insufficient elimination of acids by the kidneys. Pediatricians have found that two of the most efficient measures in the treatment of acidosis are injections of glucose and transfusions.

PROGNOSIS

Because of the very nature of the condition and the inaccuracy in diagnosis, the outcome in any case is always doubtful. The only encouragement lies in the probability that many a child has recovered from an unrecognized adrenal hemorrhage. Diagnosis of the syndrome during life should have a beneficial effect on the mortality rate both because of early recognition and treatment, but we must not be too optimistic as the infant may survive the hemorrhage only to die eventually of acute adrenal insufficiency. Our hope lies in the treatment with potent cortical extracts.

Death may occur within a few hours or days but, on the other hand, may be delayed for weeks as in Morison's patient (54) who died on the 20th day and Krahulik's who succumbed on the 40th.

SUMMARY

An *intra vitam* diagnosis of adrenal hemorrhage in the new-born may be made on the basis of a definite syndrome. This consists of two groups of symptoms: those due to acute adrenal insufficiency and those produced by internal hemorrhage. Either one of these may predominate.

Acute insufficiency symptoms consist of acute onset, high temperature, rapid respirations, petechial or purpuric rash, cyanosis and metabolic changes—especially hypoglycemia. Associated with these are gastro-intestinal and nervous disturbances.

These may be accompanied or masked by signs of internal hemorrhage (shock, collapse, weak pulse) and local signs of abdominal distress, distention and the presence of a mass in one or both kidney regions.

Five cases are reported in which an *intra vitam* diagnosis was made of adrenal hemorrhage in the new-born. Upon the basis of the syndrome presented in these cases an analysis is made of 81 cases of the condition in both new-born and infants.

Suggested therapy consists of intravenous transfusion of blood, injections of glucose and the administration of a potent adrenal cortical extract.

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GLYCOPENIA: THE EFFICACY OF HIGH FAT DIETS IN THE TREATMENT OF CHRONIC HYPOGLYCEMIA*

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The classification of diseases of the ductless glands has hinged upon the recognition of states of over- and under-function. Thus exophthalmic goiter represents an excessive activity of the thyroid hormone while its antithesis, myxedema, is the consequence of deficient thyroid activity. The clinical syndromes of hyper- and hypo-function are rapidly becoming clarified for each of the members of the hormonopoietic system. It is of historical interest that the recognition of the clinical syndrome has sometimes preceded its experimental reproduction. Thus gigantism was long suspected as due to an exaggerated activity of the anterior hypophysis before Evans produced it experimentally in rats by injections of a potent anterior pituitary-growth-hormone. In the case of the parathyroids, however, the recognition of clinical hyperparathyroidism (osteitis fibrosa cystica) by Barr and others, was the logical outcome of Collip's isolation of the parathyroid hormone and the experimental production of hypercalcemia in dogs by overdosage with extracts of the parathyroids. A similar sequence of events has followed the discovery of insulin. Although the relationship of diabetes mellitus to pathological alterations in the islands of Langerhans was postulated by Opie many years before the insulary hormone was isolated, its exact status as a hypofunctional state of the internally secreting portion of the pancreas depended on the relief of diabetes by supplementary therapy with insulin. It was inevitable that the opportunity to test this hormone clinically and experimentally would ultimately shed light on the effects of overdosage and thus lead to the recognition of the clinical state of hyperinsulinism.

The similarity in the symptomatology of glycopenia resulting from insulin overdosage to the syndrome presented by certain individuals led Harris (1) to investigate the glucose content in the blood stream at various hours during the day in a group of asthenic patients. The results of his studies are now well known; and the feeling of weakness, tremor and emotional instability experienced by these individuals has been explained by the depression in their blood sugar. Thus was brought into recognition the new clinical entity of spontaneous hypoglycemia.

It has usually been assumed that glycopenia results only from an excessive secretion of insulin by the islets of Langerhans. Harris in his original contribution reasoned that it is possible, in view of the fact that the islet tissue of the pancreas is a hormonopoietic organ, to have not

only an insufficient secretion (resulting in diabetes mellitus) but an excessive or altered secretion which might produce the series of symptoms described. This is undoubtedly true, although, in addition to hyperinsulinism, there are many other possible etiological factors capable of inducing a spontaneous glycopenia. As is now well known, the chief source of the blood-sugar is the store of glycogen in the liver (although when food is being absorbed from the intestine it can be assumed that the sugar content of the blood stream is augmented from that source directly). The liver not only is the sole organ where gluconeogenesis occurs, but it likewise acts as a storage depot for glycogen. The level at which the concentration of glucose in the blood stream is maintained results from the balance between two opposing factors, the consumption of glucose by the tissues and the production of glucose by the liver. The upward level of the blood sugar, then, is regulated by the gluconeogenic function of the liver, whereas the downward regulating mechanism consists of several factors, chief among which are the food intake, exercise and the activity of the islet tissue of the pancreas. Furthermore, interference with or alteration of any of these vital processes may result in a marked reduction of the blood-sugar level. Theoretically the primary factors responsible for any diminution in the concentration of the blood sugar must be either failure of the liver in liberating glucose or overactivity of the pancreas. However, the ultimate cause of alteration in these functions may be quite diversified.

It is obvious that actual destruction of a large amount of hepatic tissue will so hinder the formation of glycogen that a glycopenia will ensue. Fortunately approximately eighty per cent of the liver can be destroyed without altering its glycogenic function, but as early as 1874 Brock and Hoffman found that the sugar disappeared from the blood within an hour after ligation of the blood vessels going to and from the liver. Also Mann (2) demonstrated a marked drop in the blood sugar of dogs five hours after hepatectomy. Rabinowitch (3) recently referred to the marked hypoglycemia of a patient with almost complete suppression of hepatic function owing to idiopathic acute yellow atrophy of the liver, and Parnas and Wagner (4) reported the case of a girl with a tumor of the liver in whom no blood sugar was demonstrable. Nadler and Wolfer (5) cited a patient in whom, although the usual signs of hepatic insufficiency were lacking, some 70 to 80 per cent of the substance of the liver was replaced by neoplastic tissue and the remaining hepatic cells were deficient in glycogen, a condition which resulted in failure of the *sugar mobilizing function* of the liver with consequent hypoglycemia.

This loss of glycogen reserve with its consequent lowering of the blood-sugar may be brought about by an entirely different mechanism, although the end result is identical. It has been shown by various workers that the degree of hyperglycemia which develops following the injection of epinephrin is more or less proportional to the amount of glycogen in

the liver [Ritzman (6), Pollak (7), Bang (8)]. A prolonged and continuous overactivity of the adrenals might so deplete the glycogen stores of the liver as to bring about a complete exhaustion of the chief source of the blood sugar. A fatal glycopenia could thus be produced. Anderson (9) has cited just such a case in which the patient died of hypoglycemic convulsions resulting from an excessive stimulation of glyconeogenesis in the liver by a carcinoma of the adrenals.

It is also conceivable that the formation of glucose in the liver is maintained at a constant rate in the normal individual by the well-balanced activity of the adrenal glands. Any diminution in their secretion would tend to inhibit gluconeogenesis. Hypoglycemia was first noted in Addison's disease by Porges (10) in 1910; Marañon, Carrexo and Soler (11) state that in this disease hypoglycemia is always present and that the blood pressure falls concurrently with the blood sugar. Furthermore, Joslin (12) in his large series of patients with diabetes has not had a case complicated by Addison's disease; Arnett (13) was able to find only five cases in the entire literature, of Addison's disease associated with diabetes, and the diagnosis was questionable in each. Other references to the literature of hypoglycemia in Addison's disease are given by Longcope (14), but it is apparent that failure of the adrenals results in a disability of the glucose excreting function of the liver, which if sufficiently aggravated will eventually induce a reduction in the blood sugar to a level where symptoms may supervene.

Apparently, then, any interference, organic or functional, with the production of glycogen, the storage of glycogen or gluconeogenesis occurring in the liver can result in a reduction of the sugar content of the blood stream. It may be mentioned apropos of hepatic insufficiency that substances which have a deleterious effect on the liver, e.g., hydrazin, chloroform, phosphorous and arsenic, will also cause hypoglycemia.

Experience has abundantly shown that the quantity of pancreatic hormone in circulation must be carefully adjusted to the carbohydrate available for metabolism. If the latter is reduced, as in undernutrition or actual starvation, the amount of insulin is *relatively* increased to a point where glycopenia may exist. Shope (15) has found very low percentages of sugar in the blood serum of fasting men. Joslin (16) cites several patients with diabetes, none of whom had received insulin, who as a result of inanition developed marked glycopenia; and Herman (17) had had up to 1923, eight non-insulin diabetics with hypoglycemia resulting from prolonged undernutrition. Usually, however, the percentage of blood sugar in complete starvation does not fall to the level at which hypoglycemic symptoms appear, probably because the hepatic glycogen never entirely disappears. At an early stage in starvation glycogen may practically vanish from the liver but it returns later, being formed in large quantities from non-carbohydrate materials [Macleod (18)].

If, on the other hand, the available supply of carbohydrate is ex-

hausted by severe and strenuous exercise, again the amount of circulating insulin is relatively increased. The blood sugars of the competitors in a twenty-five-mile marathon run were studied by Levine, Gordon and Derick (19) and found to be moderately diminished in two runners and markedly diminished in four; percentages as low as 0.049 and 0.050 were obtained. The physical condition of the competitors who had these extremely low blood sugars at the finish of the race was closely correlated to the degree of hypoglycemia. Also Lawrence (20) has shown that exercise greatly increases the hypoglycemic action of insulin.

It is believed the extract of the posterior hypophysis acts as a direct antagonist to insulin. Consequently any diminution in the amount of circulating pituitrin would likewise result in a relative increase of the pancreatic hormone. Pituitrin is frequently administered to diabetic patients who have taken too large a dose of insulin, and Burn (21) has shown that if a subcutaneous injection of pituitary extract is given along with insulin, the fall in blood sugar usually produced by insulin is reduced, abolished or replaced by a rise. Clinically, patients classified as having a pituitary deficiency are occasionally seen, in whom the glucose tolerance curve is extremely flat, indicating a partial failure of neutralization of an increased increment of the circulating insulin. As an example of this, the "curve" obtained in such a patient is given below:

9:10	a.m.	Fasting	Blood Sugar	.079	mgm.	per	100	cc.	
9:15	"	100 gm. glucose							
9:45	"		"	"	.091	"	"	"	"
10:15			"	"	.066	"	"	"	"
11:15	"		"	"	.047	"	"	"	"

Contrawise, the frequent association of diabetes mellitus with acromegaly, a condition in which the secretion of the pituitary gland is increased, has been emphasized by Cushing and others (22). Colwell (34) in an exceptionally good review of the literature on this subject states that the diabetes which so frequently accompanies acromegaly resembles ordinary diabetes mellitus in all respects.

Finally, spontaneous hypoglycemia has been noted in diabetic patients [Joslin, Campbell and Macleod (23)] the cause of which is unknown. It is however, probable that this condition like the glycopenia resulting from exercise and distubances in the pituitary secretion follow mere *relative* increases in the amount of available insulin, depending on the failure of various factors extraneous to the pancreas.

Probably the vast majority of instances of spontaneous hypoglycemia result from an actual increase in circulating insulin or a secretion by the pancreas of an altered insulin, caused either by organic or functional overactivity of the islets of Langerhans. The morbific factors in such an excessive activity may be either neurogenic or the result of anatomic changes in the pancreas itself. Following the analogy of other ductless gland diseases, tumors of the islet cells—adenoma and the like—might be expected to give rise to a syndrome in some respects the reverse of diabetes.

Warren (24), in 1926, brought the total of the tumors of the pancreatic islets to 20, and since the appearance of his article, other instances have been reported. The case reported by Wilder, Allan, Power and Robertson (25) is the first case in which clinical data, chemical studies and pathological examination have been correlated. The patient noticed sudden attacks of weakness, faintness and paresthesia, beginning about 20 months before exitus. These symptoms increased in frequency and severity until finally death ensued. An islet cell carcinoma with metastases to the liver was found at autopsy. Insulin was found in these secondary growths.

This report was soon followed by other descriptions of islet cell tumors associated with symptoms of an oversupply of insulin. Thalheimer and Murphy (26) found low blood sugars in a patient suffering with carcinoma of the islands of the pancreas; and McClenahan and Norris (27) described a case in which the blood sugar was found to be 40 mgm. per cent. The patient died about 70 hours after admission. Necropsy disclosed an adenoma of the beta cells of the islands together with a marked hypertrophy of the islets in the remainder of the pancreas. Howland, Campbell, Maltby and Robinson (28) cite a patient whose course was extremely erratic; blood sugar determinations taken every hour of the twenty-four varied from 0.040 mgm. per 100 cc. to 0.150 mgm. Study of the patient led to diagnosis of the cause as an islet cell tumor of the pancreas. Operation revealed a slowly growing carcinoma of the islets, which was removed. The patient recovered and has since been entirely free from attacks.

Nor is it necessary that tumors be responsible for the increase in insulin secretion, for like the syndrome of Graves' disease resulting from hyperplastic changes in the thyroid gland, instances have been reported in which hyperplasia of the islet tissue existed. Thus low blood sugars were found by Gray and Feemster (29) associated with islet cell hyperplasia, without tumor formation, in the infant of a woman suffering from severe diabetes.

However, hyperinsulinism may exist without any anatomic alteration of the pancreas, a phenomenon not surprising since the opposite condition, diabetes mellitus, may likewise occur without visible change in the islands of Langerhans. To be sure, in most of the cases of spontaneous glycopenia reported in the literature, examination of the pancreas was not attempted. However, an exploratory laparotomy was performed in one of the two cases cited by Allan (30) and a normal appearing pancreas was found. Finney and Finney (31) resected a portion of the pancreas which was without demonstrable overgrowth, in a case of spontaneous hypoglycemia with at least temporary relief. A similar operation failed to relieve the symptoms of a patient studied in the Stanford University Clinic. Possibly the removal of additional islet tissue might result in permanent benefit. However, these various cases permit the assumption that spontaneous glycopenia can occur as a result of an hyperinsulinism without demonstrable pancreatic disease.

In the patients responsible for the original description by Harris, those cited by Cammidge (32), or those detailed by Winans (33), the pancreas has not been examined, nor is it probable that actual organic changes existed since these various patients responded well to medical treatment. Other evidence of islet overgrowth was entirely lacking. Possibly most of the milder instances of spontaneous glycopenia are cases of this kind, many of which have heretofore been dismissed with such diagnoses as hysteria or epilepsy or schizophrenia. However, hypoglycemia can be recognized with ease, although determination of the exact cause is difficult and occasionally impossible.

The symptoms of glycopenia are remarkable in their variation. In the first place some individuals seem to be exceedingly tolerant of a low blood sugar level. Cammidge (32) states he has observed patients whose blood sugar frequently dropped to as low as 40 mgm. per cent, yet they appeared to be healthy. On the other hand, patients with appreciably higher blood sugar figures suffered from symptoms which seriously interfered with their comfort or occupations. There is one complaint which is almost constantly heard. Nearly all patients in whom a spontaneous glycopenia occurs state that they tire easily or are constantly fatigued. In addition there may be weakness, pallor, tremor, dizziness, emotional instability, various forms of headache, loss of ability for sustained effort and mental concentration, and convulsions. Other symptoms ascribed to the glycopenia, especially by Cammidge, are cyclical vomiting, bilious attacks and, in certain instances, the vomiting of pregnancy. Griffiths (35) after studying nine patients varying in age from 6 weeks to 8 years, concludes that in convulsions in children there is probably a frequent association between this disorder and the existence of a low blood sugar content and that at least in some instances the causative relationship of hypoglycemia to convulsions may be reasonably assumed.

In adults the syndrome has usually occurred in slender, underweight, asthenic individuals who can perform their daily tasks only with great difficulty and quite inefficiently. There is occasionally associated with this condition a marked reduction in the basal metabolic rate without other evidence of hypothyroidism. Furthermore, these patients do not tolerate thyroid substance well. It must be admitted that at present this only adds to the confusion of the clinical picture, especially since the cause of the reduced metabolism has not as yet been satisfactorily explained.

Case I was a mining engineer, 39 years of age, whose chief complaints were nervousness, quick fatigableness and delayed recuperation. His family history was negligible. He had been a mining engineer since graduation from college.

He had had the usual childhood diseases and in addition an attack of what was supposed to have been chorea as a small child, which left him with an occasional mild contraction of the muscles of the left leg, even to the present time.

The story of his present illness is rather interesting. Several years ago in one of the mining districts it had been necessary for him to walk some eighteen miles twice a week. This frequently tired him, but on one trip after having completed approximately fifteen miles of the journey he became utterly exhausted and was quite unable to continue. After a few minutes rest he attempted to

go on, but was again forced to rest (he did not become unconscious); he then ate a bar of chocolate and immediately felt better and was able to resume his journey. He has been nervous all of his life, quite irritable, and had a definite tendency to brood. For years he had tired easily and had to drive himself to do his usual amount of work. He frequently awakened in the morning unrefreshed. Occasionally there occurred attacks or waves of transient weakness followed by rather profuse perspiration. He experienced a sense of failure and depression regarding his career although, as a matter of fact, he is quite a successful engineer.

He is a man of normal appearance, 71 inches in height and weighed 162¼ pounds undressed. Physical findings were entirely normal. The urine and blood count were normal, the hemoglobin being 102 and red count 5,272,000; white count, 5,850, with a normal differential. The blood Kahn reaction was normal. His basal metabolic rate was 5.4 per cent plus. His blood sugar, fasting, was 93 mgm. per hundred cc. and the 4½-hour postprandial blood sugar was 66 mgm. per hundred cc. A diagnosis of chronic hypoglycemia was made and he was placed on frequent high carbohydrate feedings. A week later his fasting blood sugar was 100 mgm. per hundred cc. and the blood sugar taken five hours after his noon meal was 60 mgm. per hundred cc. He was then placed on a high fat diet, consisting of 110 gm. carbohydrate, 90 gm. protein, 200 gm. fat. His weight at this time was 165¼ pounds undressed. Blood sugars taken seven days after the institution of a high fat diet were: fasting 116 mgm. per hundred cc.; 5½ hours postprandial 98 mgm. per hundred cc. The improvement in the patient's feeling of well-being was remarkable. About three weeks later the diet was changed to 100 grams of carbohydrate, 80 grams protein, 280 grams fat, giving a total caloric intake of 3290 calories. Since that time the blood sugars have varied within the following range:

Fasting	81	mgm.	per	hundred	cc.	to	114	mgm.	per	hundred	cc.
5 hrs. p.c.	97	"	"	"	"	"	117	"	"	"	"

The patient's weight increased to 168 pounds.

His basal metabolism has remained within normal limits and his symptomatic improvement has continued to be spectacular. His ability to work and to take physical exercise is if anything, now above the average.

Case II was a dentist, aged 48 years, whose chief complaints were slight transitory attacks of dizziness and the fact that he tired easily and remained tired all the time. The family and past history were unimportant. He had been a bright, athletic young adult during his college course but at about the age of 21 developed symptoms which resulted in a diagnosis of duodenal ulcer. This was later confirmed by roentgenological examination. Under treatment these symptoms subsided and eventually disappeared. By the time he had reached 29 years of age his health was very good and continued to be so for five or six years. At the age of 35 his ulcer symptoms recurred and he was again treated medically. Since that time he has had only very mild recurrent abdominal disturbances which occur usually when he is tired or nervous.

Influenza was contracted during the epidemic in 1918, and immediately subsequent to this he noticed that he tired easily; he became asthenic and quite nervous. Recently he had an attack of dizziness which necessitated his giving up work and subsequent to this he has remained idle. He was ambitionless and depressed.

This patient appeared to be quite apathetic; although 69¼ inches tall, he weighed but 132¾ pounds. Otherwise he was normal physically; the urine and blood count were normal, the hemoglobin being 89 per cent; R. B. C., 4,688,000; W. B. C., 6,400 with a normal differential. A basal metabolism test had been done previous to his initial visit here, and was found to be 32 per cent, minus, so that his local physician prescribed moderate doses of thyroid substance. The basal metabolic rate at our office was 18.9 per cent, minus. His glucose tolerance was determined; the blood sugar dropped to 58 mgm. per hundred cc. three hours after glucose administration.

The dose of thyroid substance was increased and a month later his metabolic rate was 7.8 per cent minus. He was placed on a high fat diet consisting of carbohydrates 100 gm., protein 70 gm., fat 250 gm., total calories 2930. A second glucose tolerance curve was obtained a month later; the lowest blood sugar obtained was 81 mgm. per hundred cc., occuring three hours after administration of the glucose.

In treating these inefficient, chronically tired individuals, almost immediate relief is obtained by elevating the blood sugar to within the range of normal. Consequently the obvious treatment consists in the frequent administration of carbohydrate in quantities sufficient to maintain the blood sugar at about 100 mgm. per 100 cc. or higher. This is particularly true in the acute cases, as for example, those resulting from island cell neoplasms, in which the blood sugar drops rapidly and to a level sufficiently low as to induce marked and prolonged convulsions. It may even become necessary in these latter cases to supply glucose constantly. However, as a rule, at least in chronic cases, six to eight feedings daily will restore the patient to a condition approximating normality.

Practically every investigator interested in the subject of glycopenia has utilized this therapeutic procedure with apparently satisfactory results. There have been one or two cases reported in which the symptoms were so acute that even the constant and continuous intravenous administration of glucose failed adequately to relieve the symptoms. These, however were individuals suffering from malignant disease and in whom the prognosis was extremely poor at the time convulsions supervened.

Occasionally, also, as in the first case cited above, frequent carbohydrate feedings fail entirely to relieve the symptoms. Indeed it was this apparently paradoxical condition that necessitated the seeking of other means for relieving the chronic glycopenia from which this patient suffered. It must be admitted, after all, that the administration of a high carbohydrate diet does not in any sense tend to relieve the cause of the condition, namely, an overactivity of the insulary portion of the pancreas. In fact, it has been shown by many investigators that carbohydrate is the ideal stimulus for insulin secretion. This is the basis for the almost universal increase in the carbohydrate allowance in the diets of diabetic patients, an increase which has apparently proved quite beneficial not only to the patients but to the disease as well. On the other hand, Odin (36) found that if a normal individual lived upon a rigid, low carbohydrate diet for some weeks and a liberal carbohydrate meal was then taken, hyperglycemia developed to such an extent that a diagnosis of diabetes would be warranted. Sweeney (37), too, has shown that glucose tolerance curves are postponed in dehydrated animals, that there is a definite decrease in tolerance on a protein diet but an increase in tolerance on a carbohydrate diet. Weeks, Renner, Allen and Wishart (38), in studies upon the effects of fasting and diets in epilepsy observed a remarkable hyperglycemia which developed in every case on a high fat diet but not with any of the other diets. This was confirmed by Odin (36). Conversely, Lennox (39) found that in non-diabetic subjects there was progressive lowering of the successive blood sugar curves following ingestion and injection of glucose. Consequently it is now generally recognized that if carbohydrate is long withheld, the insulin-secreting function of the pancreas falls in abeyance.

It therefore seemed logical to alter the entire regime of therapy in this

patient. The diet was radically changed to an extremely high-fat, low-carbohydrate intake. The results were most gratifying clinically and the effect on the blood sugar content was decidedly beneficial. Repeated blood sugar determinations made just prior to the evening meal while the patient was on a high carbohydrate diet averaged 63 mgm. per 100 cc. The blood sugar determinations made at a corresponding time subsequent to the initiation of a high fat diet were consistently elevated to an average of 101 mgm., and this in spite of a rather definite increase in the amount of exercise the patient took. Concurrently the patient's symptoms disappeared and he gained in weight.

With this experience in mind a similar procedure was immediately adopted with the second patient. The effect on the glucose time curve is given below:

	On General Diet	*On High Fat Diet*
Fasting	.104 mgm. per 100 cc.	.097 mgm. per 100 cc.
100 gm. glucose		
½ hr. later	.190 " " " "	.208 " " " "
1 hr. "	.200 " " " "	.182 " " " "
2 hr. "	.088 " " " "	.126 " " " "
3 hr. "	.058 " " " "	.081 " " " "

This type of therapy, namely, a low-carbohydrate, high-fat diet, has the advantage of affecting the fundamental cause of the glycopenic syndrome, whereas a high carbohydrate ingestion may temporarily relieve the symptoms, although actually stimulating the insulary activity of the pancreas, a condition which it seems should be avoided if permanent results are to be obtained. How soon these individuals may return to a normal diet must yet be determined, for although the patients seem well satisfied with the high fat diet, the ideal result would be to return the patient to an entirely normal condition.

There is some delay in the effect of the high fat diet in elevating the blood sugar. Consequently in acute conditions it is questionable whether such a regime would act sufficiently rapidly to be of clinical use. However, in the patient in whom the chronicity of the disturbance is well established and in whom a short delay will make little difference, there is apparently ample justification for this procedure. It furthermore has the merit of bringing about a feeling of well-being which is not surpassed and in some instances not equalled by that obtained with frequent high carbohydrate feedings, nor must the patient's appetite approach the Gargantuan proportions so often necessary to eat six or eight times daily. Finally, the fats have a definitely inhibiting influence on the abnormal process responsible for the glycopenic syndrome.

SUMMARY

The various causative factors, besides hyperinsulinism, producing glycopenia are reviewed.

Two cases are reported in which the hypoglycemia apparently results from primary hyperinsulinism.

It is suggested, in contrast to the usual increase in carbohydrate intake, that the diet be markedly reduced in carbohydrates and that a relatively high fat diet be substituted, in the treatment of essential glycopenia. Results in the cases reported indicate that such alteration of the dietary formula apparently has an inhibiting influence on the incretory function of the pancreas.

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HUMORAL FACTORS AFFECTING UTERINE MOTILITY*

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BALTIMORE

Most of the work thus far reported dealing with the physiological factors that regulate the cyclic variations in uterine motility has been concerned with the mechanism that retards the activity of the uterus at oestrus and which imparts to it a so-called characteristic oestral rhythm. During the interoestrus period in the rat or mouse it has been reported that the contractions occur more frequently than at oestrus yet never, so far as I am aware, has it been shown that the accelerated dioestral motility is due to the presence of any substance or substances which may stimulate the uterus to increased activity. This dioestral motility has been accounted for on no other basis than the vague inherent contractile properties of uterine muscle.

Blair (1) was the first investigator to describe this cyclic phenomenon, and some other workers have confirmed this original claim from time to time (4, 7, 8, 19). All of this work was performed on the excised uterus, and only recently Durrant and Rosenfeld (6), also using the excised rats' uterus, have again confirmed the original findings of Blair. They specifically call attention to the fact that the frequency of the contractions is the only manifestation of cyclic activity, and that no importance can be attached to the amplitude of the contractions. So the view persists, it seems, that oestrin, the immediate hormone of oestrus, exerts a retarding effect on the inherent frequency of the spontaneous uterine contractions (see Frank, Bonham and Gustavson, 7; also 2 and 5).

Recent experiments on the uterus *in vivo* in the unanesthetized animal make such a view no longer tenable, however, and indicate, on the contrary that oestrin is the only humoral agent yet discovered which normally imparts motility to the uterus, and that in its absence profound and complete quiescence supervenes.

THE CAUSE OF POWERFUL UTERINE CONTRACTIONS AT OESTRUS

In some experiments performed on the uterus *in situ*, we have had occasion to remove the ovaries from rabbits whose uteri were showing activity which is characteristic of oestrus (14). Records that were made soon after castration revealed that only one to two days elapsed until the uterus became completely quiescent. In view of the work to which reference was made above, it is important to note that the removal of the ovaries during oestrus did not free the uterus of a retarding influence, but that the effect was actually the reverse. A stimulus to all activity was re-

*The following paper is written to correlate briefly one phase of the results that have accumulated during a series of studies on the uterus which have been reported in the American journal of Physiology, in volumes 92, 94, 97 and 98.

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moved. Four to six days later liminal amounts of oestrin (Theelin, 2-5 r. u. per kilogram of body weight) were administered intravenously over a period of eight hours. In no instance was any effect on the uterine motility observed until 10-15 hours had elapsed after the first injection, and maximal activity was never attained until twenty-four hours or more had passed. Subsidence of the effect occurred in two to four days. In other words, oestrin in these small amounts has a long latency, and requires a relatively long time for its action to cease. This is in striking contrast to the immediate effect of oestrin that one observes when it is added to a bath in which a piece of the isolated uterus is suspended (3).

The lack of uniformity of the results reported in the literature has been discussed elsewhere (14) and it is sufficient to indicate here that it is no doubt significant that Theelin and Estrogen are the only agents that in our experience have ever induced activity in quiescent uteri *in vivo*. Pituitrin, pitocin, gynergen, and histamine (0.0025-0.01 mgm. intravenously) have never had any discernible effect on the quiescent uterus of the unanesthetized rabbit whereas they are exceedingly potent when the uterus is spontaneously contracting (13). A striking demonstration moreover of the specificity of the materials with which we are dealing is to be seen in recent work in which we were unable to elicit any uterine response whatever in sensitized rabbits whose uteri were quiescent whereas the sensitized, spontaneously contracting uterus gave a profound anaphylactic response (18). We may conclude, it seems, that oestrin is indeed specific, and is a causative agent for the initiation and maintenance of the powerful uterine contractions seen at oestrus.

WHAT ARE THE MOTILITY-INHIBITING MECHANISMS?

Inasmuch as one principle (oestrin) has been shown to stimulate uterine motility and a deficiency of it to cause uterine quiescence, it should be profitable to consider what mechanism or mechanisms there may be that actively tend to diminsh uterine contractility, and so to check the stimulating action of oestrin under certain physiological conditions.

It is generally agreed that the inactivity of the uterus during pregnancy, when large amounts of oestrin are present in the blood, may be attributed to the presence of the corpus luteum. Knaus has been the most ardent proponent of this view (9). By means of studies on the sensitivity to pituitrin of a uterine horn from a non-pregnant rabbit, he has indirectly demonstrated the motility-inhibiting effect of a corpus luteum extract when it is injected into that rabbit a day before the uterus is excised and subjected to pituitrin treatment. Our own experiments on the uterus *in situ* corroborate the view that the corpus luteum directly or indirectly inhibits uterine contractions, but here again we must add certain information that has come to light through the use of the uterine fistula technic.

We have recently shown that marked uterine motility usually precedes coitus in the rabbit; that within the space of a few hours *post coitum*

and preceding ovulation an abrupt cessation of this motility occurs, and that the uterus remains quiescent until the termination of a period of pseudopregnancy [15-21 days after sterile coitus (11)]. It appears that the onset of this effect precedes any possible effect of a corpus luteum since it occurs before ovulation. The question arises, therefore, whether or not the quiescence of later pseudopregnancy in the presence of the corpus luteum is like that which exists soon after coitus, before this structure is formed? To test this we have performed the following experiments (12): Theelin was injected into female rabbits immediately after they had received the male, in an attempt to override the onset of quiescence as soon as it appeared. This it was possible to do with as little as 5 r. u. of Theelin per kilogram of body weight, provided the hormone was administered on the first day *post coitum*. Maximal uterine activity was seen on the second day, at which time the uterus is normally quiescent. We found, however, that 600-1100 r. u. per kilogram given after the fourth day were utterly without effect on the quiescent pseudopregnant uterus. Clearly, a difference in the susceptibility to Theelin on the first and after the fourth day *post coitum* was demonstrated in these experiments. That the difference is due to the presence of the corpus luteum after the fourth day we can as yet only infer, for want of adequate replacement therapy experiments. Nevertheless we have shown (12) that by removal of both ovaries during this stage of pseudopregnancy the source of the active inhibiting agent is also removed, for a small amount of Theelin is now effective in eliciting marked activity where before, quantities failed.

An accounting must still be made, however, for the quiescence that sets in soon after coitus in the rabbit. That it is a functional or an active inhibition may be seen from the following considerations: When the oestrin influence is removed, as after the ovaries are removed, or replacement therapy discontinued, the decrease in uterine activity takes place only gradually, requiring about two days for the attainment of the quiescent condition; but when an oestral rabbit is allowed coitus, the marked activity most characteristic of oestrus is lost with great rapidity. The uterus becomes quiescent in seven hours or less. Obviously one could not explain such a sudden suppression of uterine activity solely on the basis of the removal of the influence of oestrin. We have already called attention to the fact that this change may be hypophyseal in origin (11). It is suggestive, moreover, that this effect may be exactly duplicated with whole urine of pregnancy (13). But still more striking than this are three unpublished experiments which were performed at the University of Pennsylvania, in collaboration with Dr. M. H. Friedman, and which are being further studied at the present time. Three rabbits were taken whose weights were 2.8, 3.7 and 3.8 kilograms, respectively. All three showed marked uterine motility at the time that each received some of the so-called "luteinizing hormone" of Parke Davis & Co., in a quantity which was known to be just liminal for ovulation in a 3-kilogram rabbit. The

uteri became quiescent in two to four hours in all three instances. No further records were made; the next day the rabbits were sacrificed. It was found at autopsy that the small rabbit (2.8 kgm.) had ovulated and the two large ones (3.7 and 3.8 kgm.) had not, nor had they any "blood follicles." Yet singularly enough the uterus of each one had become quiescent in two to four hours following the single intravenous injections. This is too small a series of rabbits to permit us to attach great weight to this finding, but it is indeed suggestive that the quiescence of the uterus which precedes ovulation may be attributed directly to the *causa prima* of ovulation.

DISCUSSION

From the standpoint of an endocrinologist, all the requirements of replacement therapy have been met in our experiments dealing with the influence of oestrin on uterine motility. Activity, which is characteristic of oestrus, and inactivity characteristic of anoestrus, has been demonstrated. A regular and constant deficiency syndrome has invariably followed complete ovariectomy, and these effects have been alleviated by specific substitution therapy. That the effect is specific can hardly be doubted in view of the impotency on quiescent uteri of even the accepted oxytocic drugs as they have been determined on the excised uterus. Even the high degree of sensitivity ordinarily associated with true anaphylaxis is wanting except when the sensitized uterus is spontaneously contracting, as in does that are in heat (*post partum*).

But how can there be such a wide discrepancy between the results of these *in vivo* experiments and of the work of previous investigators who employed the isolated organ? Admittedly, the saline bath is wholly artificial and cannot be expected to meet the deficiency caused by loss of circulating blood, loss of nerve supply and the effect of trauma. Still other factors could be mentioned, such as the inadequacies of "regulated" temperature, of oxygen supply for the oxygen demand of a mass of tissue that has been deprived of its circulation and most important, perhaps, the limit of time imposed when the isolated organ is used. It is just such considerations as these that would compel one to look askance at the reports of these investigations were it not for the fact that a general agreement runs through them. Indeed, Parkes points out after a survey of this work (11) that "The general conclusion is reached that during dioestrus the uterus shows rapid feeble contractions, while oestrus is characterized by fewer but much more powerful contractions." Such a conclusion requires considerable allowance be made for the fact that although most studies of cyclic activity show a retarded uterine motility during oestrus, Brouha and Simonnet (3) find (as Parkes points out on the same page as the above quotation) that if one adds oestrin to an isolated quiescent uterus, activity is at once imparted to that tissue. Conversely, lavage of a contracting uterus excised during oestrus does not remove an inhibiting agent but, on the other hand, induces full quiescence. It will be seen that

this last work appears to accord with ours, but because of the rapidity with which the effects are achieved it is evident that we must seek further than the apparent physiological reason for an explanation of the results of Brouha and Simonnet. The critical work of Van Dyke, Bailey and Bucy (16) is probably adequate to show where due allowances have not been made by those who use the excised uterus technic. These workers have shown, for instance, that cerebro-spinal fluid is oxytocic only when it is hypertonic with respect to the calcium ion; 0.2-0.7 millimol excess of the calcium ion is sufficient to give a marked oxytocic effect on a quiescent uterus.

We have mentioned in the introduction that there has never been offered an adequate explanation of the interoestral activity which has been so frequently described in the rat. If it should be true that there is, as Parkes points out, rapid but feeble activity at this time, one wonders what role the recently discovered inhibiting mechanism might play. We may only surmise on this point, yet is it not barely possible that here where the cycles are so rapidly recurrent that the corpus luteum is said to be non-functional and is merely a "histological ornament," that some influence may be exerted by this other motility inhibiting mechanism? It may be recalled that Brambell and Parkes have shown the stimulus for oestrus is given a full forty-eight hours before its expected advent, and at a time after the mid-interoestrum when feeble, rapid contractions are present. The possibility that this mechanism is a factor of any consequence is purely speculative but since it is a point hitherto unnoticed, it may be one with which to be reckoned in future studies.

SUMMARY

Previous work based on the excised uterine strip technic has indicated that slow uterine contractions at oestrus are attributable to oestrin, and that in the absence of this hormone the uterus contracts more frequently; the amplitude of the contractions is said to be independent of the action of oestrin. Recent work based on the uterine fistula technic does not corroborate this view. It shows that powerful uterine contractions usually occur at oestrus; that little or no activity is seen in anoestrus, and that castration, and hence the absence of oestrin, is invariably followed by complete quiescence of the uterus in one to two days' time. Replacement therapy with oestrin restores again activity which is like that seen at oestrus. Evidence is cited that some mechanism other than that attributable to the corpus luteum exerts an inhibiting influence on the rhythmic contractions of the uterus. The probable source of this inhibiting agent (possibly the hypophysis) is discussed.

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Abstract Department

Effect of adrenal cortex extract on the development of the testes (Der Einfluss der Hyperinterrenalisierung auf die Entwicklung der Männlichen Geschlechtsorgane). Asher, L. and O. Klein, Klin. Wchnschr. **10**: 1076. 1931.

The authors find that injection of an adrenal cortex extract into male rats brings about an increase in the size of the epididymis, the seminal vesicles and the penis. The effect was strengthened by simultaneous injection of thymocresin. They confirm Müller in finding that the adrenal cortex extract retards the development of the sex apparatus of the female rat.—R. L. Zwemer.

Influence of adrenalin on nitrogenous metabolism and glycemia of hypophysectomized dogs (Influencia de la adrenalina sobre el metabolismo nitrogenado y la glucemia en la insuficiencia hipofisaria). Braier, B., Rev. Soc. argent. de biol. **7**: 283. 1931.

Intravenous injection of adrenalin on the fourth day of complete fasting reduces urinary elimination of nitrogen in hypophysectomised dogs (4%) and in controls (9%); creatinin is also reduced and blood urea rises. Blood sugar rises less in the operated than in the control animals. In animals not fasting adrenalin produces a more marked hyperglycemia in hypophysectomised dogs than in controls.—J. T. Lewis.

Epinephrin action in relation to the hydrostatic pressure effect on the contraction of cardiac muscle. Cattell, M. and D. J. Edwards, Am. J. Physiol. **96**: 656. 1931.

The stimulating action of increased hydrostatic pressure on the tension developed by cardiac muscle is augmented by the presence of epinephrin. This augmentation is greater than the stimulation produced by epinephrin alone, indicating a synergistic action between these two agents. Through the combined action of pressure (1200 to 1600 pounds) and epinephrin (1:250,000) the average value for the tension developed was increased 70.9% in the case of the auricles and 121.4% in the case of the ventricles.—Authors' Summary.

The mechanism of epinephrine action; changes in liver glycogen and blood lactic acid after injection of epinephrine and insulin. Cori, G. T., C. F. Cori and K. W. Buchwald, J. Biol. Chem. **86**: 375. 1930.

Blood sugar, blood lactic acid, and liver glycogen were determined in well fed rats at various time intervals after subcutaneous injection of epinephrine, insulin, or both hormones. Fifteen minutes after the epinephrine injection liver glycogen was lower, after 1 hour it was the same, and after 3 hours it was higher than in control animals. Blood lactic acid which was augmented after 15 minutes and after 1 hour, had returned to normal 3 hours after the injection, while blood sugar was still elevated at that time. On the basis of the available data it was calculated that the sugar set free in the liver in the first hour of epinephrine action amounted to only one-fourth of what a rat can use per hour. This confirms the previous contention that decreased utilization of blood sugar plays an important rôle in epinephrine hyperglycemia. Fifteen minutes after the insulin injection liver glycogen and blood sugar were unchanged, while after 1 hour both had diminished. When insulin and epinephrine were injected, the former prevented the decrease in liver glycogen and the increase in blood sugar regularly observed after the injection of the latter. Insulin is therefore an inhibitor of the hepatic glycogenolysis accelerated by epinephrine. Insulin has, however, very little effect on the increase in blood lactic acid resulting from the injection of epinephrine.
—Authors' Abst.

The effect of adrenaline on muscle glycogen. Corkhill, A. B. and H. P. Marks, J. Physiol. **70**: 67. 1930. Abst., Chem. Absts. **25**: 3083.

Adrenalin alone and adrenalin and insulin together were administered to decapitated cats whose viscera had been removed, and the subsequent changes

in carbohydrate content of blood and muscles observed. It was concluded that adrenalin causes discharge of glycogen from resting muscle. Part of this glycogen appears as lactic acid and another part as some unknown substance which is non-reducing or has a lower reducing power than glucose does, or it fails to be extracted for analysis by the methods used. A similar discrepancy was noted when insulin and adrenalin acted together.

Cortical adrenal extract and sensitiveness of adrenalectomized rats to intoxication (Extracto corticosuprarrenal y resistencia de las ratas suprarrenoprivas a los tóxicos). Houssay, B. A. and A. O. Marenzi, Rev. Soc. argent. de biol. **7**: 158. 1931.

Swingle and Pfiffner's extract injected into adrenalectomized rats suppresses hypersensitiveness to morphine and histamine.—J. T. Lewis.

Mobilization of the muscle glycogen by adrenalin and the resynthesis of lactic acid in the liver. Geiger, E., Biochem. Ztschr. **223**: 190. 1930. Abst., Chem. Absts. **24**: 5362.

Studies on the glycogen content of the 2 gastrocnemia muscles in the frog show that adrenalin injected into the lymph sac causes the mobilization of the muscle glycogen which is independent of the liver, since it occurs also in dehepatized animals. The extirpation of the liver does not affect the glycogen content of the muscles, at any rate not in frogs which have been operated on 3-4 days previously. In the perfused isolated leg muscles of frogs or dogs the addition of adrenalin does not cause an increase in the sugar but the lactic acid output is greater. It is contended that the muscle glycogen is changed to lactic acid under the influence of adrenalin because adrenalin mobilizes muscle glycogen and increases the lactic acid output of isolated muscles but does not increase the blood lactic acid content after the removal of the muscle glycogen depot. An injection of adrenalin does not produce glucosuria in dehepatized frogs but produces an increased excretion of lactic acid in the urine, so that in the absence of the liver the lactic acid can neither be retained nor resynthesized. Similar results are obtained on normal frogs after their hibernation when adrenalin produces not glycosuria but lacticiduria, so that apparently only a liver containing glycogen can synthesize the lactic acid. Furthermore, the frogs after hibernation excrete lactic acid even without adrenalin treatment, which is interpreted to show that the lactic acid produced in the muscles goes normally to the liver, but when this is glycogen-proof, as at the end of hibernation, it cannot completely resynthesize the lactic acid. The liver is therefore regarded as the most important organ for the resynthesis of lactic acid in the organism.

On effect of uni and bilateral suprarenalectomy upon some blood constituents of rabbits. Ohguri, M., Tohoku J. Exper. Med. **17**: 378. 1931.

The total nitrogen, the protein nitrogen, the non-protein nitrogen, the preformed and total creatinine, the uric acid, the inorganic phosphorus, the blood sugar, the haemoglobin, C1 (as NaC1), and water were determined in the blood, before and after single and after second suprarenalectomy, that is, loss of both the main suprarenal bodies. The rabbits survived the double suprarenalectomy indefinitely. The determinations yielded no difference in the concentration of the constituents in the three sets of experiments.

—Author's Summary.

Influence of adrenaline on the blood and organ lipoids (Einfluss des Adrenaline auf die Blut- und Organlipoide). Page, I. H. and L. Pasternak, Biochem. Ztschr. **232**: 295. 1931. Abst., Chem. Absts. **25**: 3088.

After injecting 0.3 mgm. adrenalin every 15 minutes for 4 hours into rabbits there was found a diminution in the phosphatides, cholesterol, fatty acids and total fat of the serum, while in the liver there was an increase in fatty acids, cholesterol and total fat. In the kidneys the phosphatides, fatty acids and total fat were diminished. In the brain the phosphatides were diminished, while the cholesterol was increased, and the fatty acids became somewhat less unsaturated. In the heart also the phosphatides and cholesterol were diminished. The effect of adrenalin is the same on lipemic rabbits, though this may be marked by the progressing lipemia. Insulin and

adrenalin both cause a lowering of the lipoids in the serum, but the effect of the former is somewhat more pronounced. So far as the influence on the lipoids of organs is concerned, with very few exceptions the two hormones do not act in the same way.

The sensitization by cocaine of gastric and uterine smooth muscle to the inhibitory action of adrenin. Rosenblueth, A., Am. J. Physiol. **98:** 186. 1931.

The action of cocaine on the effects produced by adrenin on excised intestinal and uterine muscles was studied. The results were contradictory. The method is criticized and deemed inadequate. The same action was studied on the cat's stomach and uterus in situ. Cocaine augments the inhibitory effects of adrenin on the movements of the stomach and of the non-pregnant uterus of the cat, thus sensitizing these smooth muscles as it does all other studied up to the present.—Author's Summary.

The so-called influence of the suprarenal medulla on alimentary hyperglucemia (Presunta influenza della midala surrenale sull'iperglicemia alimentare). Racchiusa, S. and A. Crisera, Boll. d. Soc. ital. di biol. sper. **5:** 993. 1930. Abst., Chem. Absts. **25:** 2181.

Dogs subjected to the complete or incomplete ablation of the suprarenal capsule showed, immediately after the operation, a marked lowering of temperature which reached 34-35° in some cases. After the complete ablation of the suprarenal medulla, and in some cases after the removal of the greater part of the cortex, not only was there no hypoglycemia but in some cases there was a tendency toward hyperglucemia after the administration of glucose.

Studies on the cerebral circulation. Action of adrenin (Etudes sur la circulation cérébrale. L'action de l'adrénaline). Riser, M. and R. Sorel, Compt. rend. Soc. de biol. **104:** 297. 1930.

Over 20 dogs were trephined and the reaction of the cerebral vessels followed by direct observation. Adrenin was given by artery, vein, subcutaneously, and intra-muscularly, in large and small doses. In no case did a spasm of the vessels, such as appears in the peripheral arteries, occur either during the injection or later.—J. C. D.

Further study on the influence of an aqueous extract of suprarenal cortex on the growth of carcinoma, sarcoma, and melanoma in animals. Sugiura, K., Am. J. Cancer, **15:** 707. 1931.

In view of the interest which has been developed in connection with the extract of suprarenal cortex and in internal secretion therapy in cancer, the writer investigated the therapeutic effects of an aqueous extract of sheep suprarenal cortex, prepared according to the method of Coffey and Humber, on the Flexner-Jobling rat carcinoma, the Sugiura rat sarcoma, the Bashford mouse carcinoma No. 63, a transplantable mouse melanoma, and the Rous chicken sarcoma. The extraction of cortical substance was done at from 60°C. to 85°C. Single or repeated subcutaneous or intramuscular injection of the aqueous extracts of the cortical tissues showed no curative, retarding or accelerating influence upon the tumor growth. Injection of the suprarenal cortex extracts brought about neither early tumor ulceration nor prolongation of life in the tumor-bearing animals. Injection of the aqueous extracts of suprarenal cortex did not have any appreciable effect in checking the growth of spontaneous mammary carcinomas of mice. The effects of the aqueous extracts of sheep suprarenal cortex has been also studied upon patients suffering from advanced cancers, and no beneficial results have been observed.—Author's Abst.

Influence of the piqûre of Cl. Bernard upon the epinephrine discharge, the blood sugar content and the blood pressure. Yen, T. J., T. Kaiwa and M. Wada, Tohoku J. Exper. Med. **17:** 345. 1931.

Bernard's puncture of the floor of the fourth ventricle was made in non-anaesthetized, non-fastened and non-laparotomized dogs. The epinephrine output rate, the blood sugar, the mean arterial blood pressure, and the heart and respiration rate were simultaneously estimated. The piqûre occasioned

an abrupt elevation in the blood sugar content, roughly from 0.1-0.12% to 0.15-0.2%; the peak was reached a few minutes to thirty minutes after piqûre (after piqûre blood samples were taken as a rule 5, 15, 30, 60 minutes), and the hyperglycaemic period lasted about a half hour to two hours. The epinephrine secretion rate was also accelerated; from the normal, quiet value of 0.00001-0.00002 mgm. per kilo and per minute from one side gland it was augmented and reached as high a value as 0.001-0.005 mgm. per kilo and per minute, a few minutes or rather frequently thirty minutes after piqûre. The hyperepinephrinaemic phase extended about two to three hours, and the total quantity of epinephrine secreted by piqûre was estimated as 0.013-0.12 mgm., mean 0.05 mgm. from both glands. Further, an average of the amount of epinephrine secreted was 0.013 mgm. per kilo in the first thirty minutes, 0.012 mgm. per kilo in the next thirty minutes, 0.015 mgm. per kilo in the second hour and 0.012 mgm. per kilo in the third; in total 0.05 mgm. from both glands. The peak of the hyperglycaemia was found sometimes simultaneously with that of hyperepinephrinaemia, in others being preceded by the latter, and in still others the reverse. Ether anaesthesia rendered largly obscure these effects of piqûre upon the blood sugar content, the epinephrine secretion and the blood pressure.—Authors' Summary.

On the relations between strontium and parathyroids (Sui rapporti tra Stronzio e Paratiroidi). Comel, M., Archive dello Instituto Biochimico Italiano, **2**: 669. 1930.

According to the author strontium salts, besides causing a characteristic poisoning of the nervous system, cause modification of the Ca:P ratio. This action was also found by Cagnetto, who considers that rickets may be caused by strontium poisoning on account of the altered Ca:P ratio. The author found that strontium poisoning can be produced with lighter doses than required by normal animals, if given to parathyroidectomized animals. Again these last do not recover so well nor so quickly as the normal animals when strontium is discontinued. The parathyroids of animals treated with strontium showed a hyperplasia, as may occur in rickets. The author believes there may be a compensatory hyperplasia of the parathyroids to counteract the influence of strontium on the Ca:P ratio. This change would also explain the quick recovery of the animals as soon as the strontium is discontinued. It might also be that the hyperplasia with increased blood flow indicates the acquisition of a greater detoxicating ability of the glands, though their calcium ruling function seems to apply better to the case.—G. V.

An unsuccessful attempt to demonstrate humoral action of "vagus substance" in the circulating blood. Freeman, N. E., R. A. Phillips and W. B. Cannon, Am. J. Physiol. **98**: 435. 1931.

In an effort to demonstrate the presence of vagus substance in circulating blood, experiments were made on 43 cats under different anesthetics or decerebrated. In order to obtain as much vagus substance as possible, the entire vagal supply to the smooth muscle of the alimentary canal was used as a source, and in some experiments the supply to the heart and lungs was added or used alone. The portal vein was connected to the inferior cava in order to avoid possible destructive action on the vagus substance by the liver. A variety of test organs—iris, submaxillary gland, heart, tongue, stomach and intestines—was employed, some of them sensitized by previous denervation. Physostigmine was given also as a means of perhaps enhancing the action of vagus substance. The results were wholly negative.—Authors' Summary.

The effect of gland preparations on the metabolism of rabbit (Stoffwechselversuche mit Hormonpräparaten an Kaninchen). Horsters, H., Ztschr. f. d. ges. exper. Med. **73**: 167. 1930.

Phosphorus, sodium chloride, calcium metabolism and albumin and cholesterol content of the blood were carefully studied in rabbits during 9 days (3 day preliminary period, 3 days daily injection of gland preparations, and an after period of 3 more days). The gland preparations used were: präphyson (anterior pituitary), hypophysin and pituigan (posterior lobe of hypophysis), progynon (oestrin), suprarenin, thyroxin and parathyroid extract Henning. Anterior pituitary extract evoked a 500% increase of urinary excretion

of phosphates; posterior pituitary extract administration resulted in retention of phosphates and sodium chloride during the usual decrease of urinary flow with an after effect of diuresis and increased elimination of salts; oestrin injections were followed by an increase of calcium and cholesterin content of the blood. Other known facts are confirmed. Every gland preparation, with the exception of parathyroid extract, decreased the albumin content of the blood. As far as salt metabolism is concerned, no real antagonism could be found between any two of the investigated preparations.—Z. M. Bacq.

The effect of estrin administration on the reproductive and blood vascular systems: the thyroid, thymus, hypophysis, adrenals, kidneys, liver and spleen. Kunde, M. M., F. E. D'Amour, R. G. Gustavson and A. J. Carlson, Am. J. Physiol **96**: 677. 1931.

Subcutaneous injections of estrin over a period of time, varying from 6 to 17 weeks, caused a diminution of the size of the ovaries, an arrest in the development of the follicles and a relative increase in the amount of ovarian stroma. Marked hyperplasia of the uterine glands (especially the basal glands) occurs in puppies after estrin injections, but no hemorrhagic discharge from the vagina was observed. The hypophysis of the dog receiving female sex hormone for 17 weeks was smaller than the hypophysis of the control and measurements indicate a relatively greater decrease in the anterior than in the posterior lobe. Neither gross nor histopathology was observed in the arteries, heart, liver, spleen, thymus or adrenals after 17 weeks of daily doses of female sex hormone.—Authors' Summary.

Responses to injection of epinephrine in hepatic disease. Loeb, R. O., E. Shorr and H. B. Richardson, J. Clin. Investigation, **10**: 19. 1931.

In order to study the behavior of glucose and epinephrine in the presence of hepatic disease patients at rest and in the fasting state received subcutaneous injections of adrenalin in doses of 0.7 to 1 cc. Blood pressure was determined at intervals of two to three minutes for one-half hour, and at intervals of five minutes during the next half hour. Concentrations of glucose and lactic acid in the blood were made one-half, one and two hours after the injection. The results obtained were as follows: (1) The rise in blood sugar is less marked in cases of liver disease, diabetes and many other pathological states than in normal subjects. (2) The blood sugar curve after epinephrine injection is in no way characteristic of liver disease and does not appear to correspond closely to the type or degree of damage present. (3) The lactic acid content of the blood in the postabsorptive period is occasionally increased in hepatic disease. This abnormality is not limited to lesions of the liver, nor is it consistently related to the severity of the process or to the concentration of bilirubin in the blood. (4) Contrary to theoretical expectations, the lactic acid curves resulting from the administration of adrenalin are frequently lower in liver disease, diabetes and certain other pathological conditions than in normal individuals. (5) It is suggested that the abnormally small response of the blood sugar and lactic acid in liver disease and certain other pathological conditions, notably diabetes, results from an inhibition of the action of epinephrine on carbohydrate metabolism. (6) The pressor effect of epinephrine tends to be the same in normal individuals and patients suffering from liver disorders, except in cases of carcinoma of the pancreas with obstruction of the bile ducts where this effect is decreased.
—R. F. Loeb.

The effect of the removal of the suprarenals and accessory cortical tissues together upon some blood constituents of rabbits. Ohguri, M., Tohoku J. Exper. Med. **17**: 390. 1931.

In male rabbits one suprarenal gland was removed together with the accessory cortical tissues in a three stage operation. After recovery the following blood constituents were determined: total nitrogen, non-protein nitrogen, urea nitrogen, preformed and total creatinine, uric acid, chlorine, inorganic phosphorus (in serum), sugar, haemoglobin and water. Again after recovery the second suprarenal gland was extirpated, and with the animal either in still apparently normal condition or in a weakened or even a moribund state, blood was analyzed. When tested in the incomplete cortical tissue deficiency stages, either before extirpating the second suprarenal gland or

when accessory cortical mass was left behind, the blood constituents were found wholly normal. In the rabbits suffering from complete cortical tissue deficiency the following changes were found: The haemoglobin content increased, but not very considerably, the maximum being found as 24% increase over the initial. It did not tend to increase rapidly at the terminal stage. The water content diminished invariably, but slightly. It is doubtless true that the blood is concentrated in the rabbit in the complete cortical tissue deficiency. Blood sugar was found decreased in the enfeebled state of rabbits suffering from the deficiency. Total nitrogen and protein nitrogen increased in the cortical tissue deficiency. When the rabbits were apparently still more or less healthy the increase was not large. Non-protein nitrogen increased, and its degree of increase was distinctly greater than that of the total nitrogen (and protein nitrogen). When the animal was weak, the increase was also large. Urea nitrogen increased in the complete suprarenocortical deficiency in about the same ratio with the non-protein N, but in the cases of urea N there did not exist any definite relation between the symptoms and the magnitude of increase. Preformed and total nitrogen increased invariably, and the degree more or less depended upon the weakness of the animals. Uric acid increased also, but the intensity of increase was somewhat similar to that of urea N in relation to the symptoms. Chlorine decreased, and its magnitude depended apparently on the interval allowed to elapse after the complete removal of all the cortical tissues. Serum inorganic phosphorus increased in the deficiency and the increase was greater when the animals were weak.

—Author's Summary.

Carbohydrate metabolism in mongolian idiots as evidence of endocrine dysfunction. O'Leary, W. D., Am. J. Dis. Child. **41**: 544. 1931.

A low sugar tolerance was noted in 14 mongolian idiots who were receiving thyroid extract (gr. ⅕), pituitary substance (gr. ⅕) and anterior pituitary (gr. 1) daily for eight months. A high tolerance was found in four who received no treatment. The high sugar tolerance in non-treated mongolian idiots shows an endocrine imbalance and the low curve in the treated patients would seem to be due to the action of the glandular therapy.—M. B. G.

Tryptophane in blood and tissues after thyroidectomy and pancreatectomy (Triptofano de la sangre y tejidos en la insuficiencia tiroidea y en la diabetes experimental). Potick, D. and P. M. Re, Rev. Soc. argent. de biol. **7**: 163. 1931.

After pancreatectomy in dogs tryptophane increases considerably in the thyroid, increases in red blood cells and decreases in plasma and muscle. After thyroidectomy tryptophane decreases in spleen, liver, kidney, adrenal and brain; it increases in pancreas and blood plasma and has normal values in muscle.—J. T. Lewis.

Myasthenia gravis and internal secretion. Sakamoto, A., Folia Endocrinol. Japonica. **7**: 17. 1931.

The author reviewed the literature on the endocrine aspects of the disorders and added a detailed case report with autopsy findings. After the myasthenic symptoms had become manifest, a condition of vagotonia accompanied by hypoglycemia was noted. It was postulated that the sympathetic-endocrine structures were functioning defectively, hence thyroid treatment was instituted. This was followed by marked diminution of the myasthenic symptoms. At autopsy there were noted: lymphoid infiltration of the muscles, liver and adrenal glands. A few groups of large eosinophil cells were seen in the parathyroid glands. The thymus was large. The study included periodical determination of the reactions to pilocarpin, atropin, adrenalin and thyroid substance as well as direct manifestations of vegetative reactions. The study was interpreted as adding further support to the theory of endocrine etiology of the disorder.—R. G. H.

Mongolism in one of twins. Waring, J. I., Am. J. Dis. Child. **41**: 351. 1931.

According to the author, the occurrence of mongolism in one of dizygotic twins supports the view that the condition is the result of a defect in the germ plasm and not due to the general physical condition of the parents.—M. B. G.

Endocrine function of ovarian homoio-grafts and the fundamental laws of ovarian dynamics (Uber die endokrine Funktion des homoio-transplantierten Eierstocks und die Fundamentalgesetze der ovariellen Dynamik). Adamberg, L., Virchows Arch. f. path. Anat. **276:** 632. 1930.

If an ovary is engrafted into the kidney of a castrated female guinea pig and the ovary takes, an abnormal sexual cycle is established. Cornified and epithelial cells normally present only for several hours may be present for as long as two weeks. Such a prolonged oestrus may be followed by a prolonged dioestral period for several months. In the majority of cases corpora lutea are to be found in the ovary. Since large graafian follicles are also present it is concluded that the prolonged dioestral condition of the engrafted female is dependent upon the presence of corpora lutea in the graft. Ovaries were also engrafted into the kidney of females castrated as long as 4 to 7 months. There was always taking of the ovary as in freshly castrated animals, but survival of the graft in the former cases was shortened as compared with the latter. This is probably due to local influences depending upon the site of former operation: the same shortening of survival of the graft was produced in experiments in which there was unilateral castration and in which several months afterwards the ovary was engrafted in the kidney of the operated side, the ovary being removed simultaneously on the other side. It is concluded that local conditions influence the fate of the graft considerably.—A. Lipschütz.

Changes in liver glycogen in gonadectomized animals (Variations du glycogène hépatique chez les animaux chatrés). Cahane, M., Compt. rend. Soc. de biol. **104:** 447. 1930.

In guinea pigs spaying reduced the liver glycogen, while castration increased it.—J. C. D.

The preparation and properties of the gonad-stimulating hormone from the urine of pregnancy. Dickens, F., Biochem. J. **24:** 1507. 1930.

The gonad stimulating hormone is precipitated from the urine of pregnant women by saturation with ammonium sulfate. The material obtained by this method is exactly the same as that prepared by Aschheim and Zondek. It is assayed in a manner similar to the Zondek-Aschheim pregnancy test. Injection of the hormone into immature animals (mice and rats) leads to precocious sexual maturity. The hormone is active by mouth only when very large doses (40 units) are given. The extract is without effect upon the growth-rate of normal rats. Injection over a long period does not cause any detectable change in the blood cholesterol or urea contents. By the method of preparation described, the yield of active principle is satisfactory. Aqueous solutions containing up to 1000 mouse-units per cc. have been obtained, and the injection of 0.02-0.006 mgm. of the material causes the characteristic changes in female mice. On dialysis the hormone passes only very slowly through parchment, more rapidly through collodion. It is inactivated by boiling and by the action of acids and alkalies. It is not rapidly destroyed by pepsin or trypsin. In the purified solution containing 200 units per cc., the biuret reaction is faint but definite; the Millon, glyoxylic and Molisch tests are positive. No precipitate is given with trichloracetic, salicylsulphonic or picric acid, and the solution remains clear on boiling. The hormone is precipitated without loss of activity from the aqueous solutions by complete saturation with ammonium sulfate, by alcohol or acetone, by "colloidal iron" or tannic acid. A method of purification based on the use of tannic acid is described.—E. S. Young.

Separation of the male sex hormone from the female hormone, menformone (Zur Trennung des männlichen Sexual-Hormons vom Weiblichen Menformon). Dingemanse, E., J. Freud, S. Kober, E. Laqueur, A. Luchs and A. W. P. Münch, Biochem. Ztschr. **231:** 1. 1931. Abst., Chem. Absts. **25:** 2751.

Menformone behaves somewhat like an acid and in a diphasic system, benzene-alkaline 70% alcohol, it passes almost quantitatively into the latter phase. In extracting the male hormone from male urine it is found to proceed more rapidly in a weakly alkaline medium. The method of separation depends upon extracting with benzene two portions of the urine, one made alkaline, the other acid.

On the mechanism of ovulation in the rabbit. III. The rate of mechanically ruptured follicles. Friedman, M. H., Am. J. Physiol. **98**: 209. 1931.

In eight unmated rabbits the mechanical rupture of the large follicles of one ovary did not lead to the formation of corpora lutea either in the operated ovary or in the contralateral ovary. The trauma of follicular puncture, as practiced in these experiments, is not sufficient to prevent the process of luteinization when an adequate stimulus for the process is present. In the light of these results, it becomes evident that mere follicular rupture is in itself not sufficient to cause luteinization.—Author's Summary.

The Reid Hunt-reaction and pregnancy (Reid Huntsche Reaktion und Schwangerschaft). Eufinger, H. and H. Wiesbader, Arch. f. Gynäk. **142**: 662. 1930. Abst., Chem. Absts. **25**: 1276.

The resistance of white mice to a lethal dose of acetonitrile is heightened by a previous series of injections of serum from a woman in the later stage of pregnancy. The hormone from the anterior lobe of the hypophysis increases the acetonitrile resistance enormously and the increase of resistance does not seem to be dependent on the absolute quantity of the hormone. Preparatory treatment with ovarian hormone also increases the acetonitrile resistance, therefore, cannot be attributed solely to the increased presence in the serum of pregnant women of thyroxine-like substances, but it is probable that an increase of the hormone of the anterior lobe of the hypophysis and perhaps an increase of ovarian hormone are of marked importance.

Further observations on the pregnancy response of the uterus of the cat. Gustavson, R. G. and H. B. Van Dyke, J. Pharmacol. & Exper. Therap. **41**: 139. 1931.

After the repeated injection of sterile urine of pregnant women into normal and spayed cats, the following observations were made: Spayed cats exhibited uterine hypertrophy without a pregnancy-reversal. Cats with one or both ovaries intact also exhibited a marked uterine hypertrophy. The uteri contracted like those of pregnant cats only when the ovaries contained mature corpora lutea. The anatomical changes are discussed.—Authors' Summary.

Action of ovarian graft in males on the seminal vesicles (La acción del injerto de ovario en machos sobre las vesiculas seminales). Houssay, B. A., L. Giusti and L. Lazcano González, Rev. Soc. argent. de biol. **7**: 115. 1931.

Ovarian grafts in adult male guinea pigs produce considerable hypertrophy of the seminal vesicles. In castrates ovarian grafts do not delay atrophy of vesicles, therefore they act through the testicles. Implantation of pituitary also produces enlargement of seminal vesicles in intact animals but not in castrates. Daily injections of folliculin (oestrin) during 35 days produce hypertrophy of the mammary gland but have no effect on the testicles and seminal vesicles. The ovarian graft possibly stimulates the production of pituitary sex hormone which in turn acts on the testicle and by this mechanism the seminal vesicles are hypertrophied.—J. T. Lewis.

Studies on sex reversal in Amblystoma. V. The structure of ovaries of A. tigrinum subjected for long periods to the influence of a testis resident in the same animal. Humphrey, R. R., Anat. Rec. **51**: (No. 2). 1931.

Previous experiments have shown that an ovary developing under the influence of a testis resident in the same animal commonly undergoes modification to a rudimentary or vestigial structure. Such ovaries often begin reversal to functional testes (i. e., testicular lobules begin to develop) in animals under six months of age. Other ovaries at this time, however, show no development of testicular lobules, and these regenerate into normal ovaries when the testis responsible for their modification is removed. In this experiment, ovaries reduced to a known rudimentary or vestigial state were allowed to remain for longer periods (eight to fourteen months) under the influence of a testis. In these ovaries the germ cells (oogonia) of the cortex decreased in numbers, sometimes eventually disappearing almost completely; regeneration of the cortex in consequence occurred slowly or not at all when the ovary was relieved

of the influence of the testis. In many ovaries testicular lobules developed after a variable time, thus completing reversal into a testis. In others, however, lobules failed to develop. Such gonads usually had few or no germ cells in their hilar or medullary portions. With the reduction of their cortical germ cells these approached a condition of complete sterility. It is concluded that a small portion of all modified ovaries would remain in this state indefinitely.—Author's Abst.

Experimental basis of ovarian transplantation (Die experimentellen Grundlagen der Eierstocks-verpglanzung). Lipschütz, A., Abh. Grenzgeb. inn. Sekretion, **6**: 51. 1930. Rud. Novak & Co., Budapest & Leipzig.

The author summarizes his work on auto- and homoiotransplantation in the guinea-pig, with special reference to the internal environment of the organism as a whole or what he calls the fundamental laws of ovarian dynamics, i. e., law of follicular constancy and the law of puberty. The chapters of the book are: Auto- and homoiotransplantation, heterotransplantation, influence of the internal environment, the quantity of the ovary to be engrafted, the condition of the ovary to be engrafted, and transplantation of the conservated ovary.—Author's Abst.

Gastric absorption of the follicular hormone. Maino, M. M., Archivo dello Istituto Biochimico Italiano, **2**: 495. 1930. Abst., Chem. Absts. **25**: 3724.

Experiments with rats confirm the observation that the mucosa of the digestive apparatus serves well for the absorption of the ovarian hormone. The dose of hormone necessary by this route is treble that required parenterally; the gastric absorption is not influenced by the degree of purity of the solutions used. The nature of the vehicle in which the hormone is ingested affects the amount absorbed, alcohol solutions being the most active.

The sensibility of auto grafts of vaginal mucosa of guinea pigs to folliculin (Les autogreffes de muqueuse vaginale chez le Cobaye, leur sensiblité a la folliculine). Raynaud, R., Compt. rend. Soc. de biol. **104**: 284. 1930.

In a spayed animal a vaginal fragment was removed and placed under the skin in the pectoral region. Two or three weeks later if the graft persisted, the animal received 20 rat units of folliculin. The graft responded in the same manner as the normal mucosa.—J. C. D.

Variations in the sugar level in castrates (Variations du taux de la glycémie chez les castrats). Rogemont, L., Compt. rend. Soc. de biol. **104**: 256. 1930.

Young and adult cocks were castrated. There was a permanent increase of blood sugar (23-25%) over that of the controls.—J. C. D.

The production of placentomata in young rats following gonadal stimulation with pituitary implants. Shelesnyak, M. C., Am. J. Physiol. **98**: 387. 1931.

The production of placentomata in young rats following gonadal stimulation by pituitary implants and subsequent injections of basic extract of anterior lobe was uniformly successful. Controls which received amniotin (Squibb's) in place of fresh anterior pituitary implants but identical other treatment were negative.—Author's Summary.

What effect have the hormones of pregnancy on the growth of the fetus and the changes of pregnancy of the mother (Welchen Einfluss haben die Schwangerschaftshormone auf das Wachstum des Feten und die Schwangerschaftsveränderungen der Mutter)? Siegert, F., Arch. f. Gynäk. **143**: 72. 1930. Abst., Chem. Absts. **25**: 3040.

Both the ovarian hormone and the hormone from the anterior lobe of the hypophysis are increased during pregnancy. The ovarian hormone is excreted in the urine in increasing amounts as pregnancy progresses while the hypophyseal hormone is excreted in large amounts from the very onset of pregnancy and in lesser amounts as pregnancy progresses. While in early pregnancy the blood always gives a positive test for ovarian hormone, at the time of delivery the blood of the mother gave a positive reaction in 57.7% of the 52 cases

studied and the blood of the child a positive reaction in 76.5%. The content of hypophyseal hormone is the same in the blood of both mother and child and shows no decrease at the time of delivery. It is probable that the ovarian hormone plays an important role in the changes in the organism of the mother that accompany pregnancy and that it is excreted in larger amounts in the second half of pregnancy because its biologic importance is now lessened. The biologic activity of the hypophyseal hormone during pregnancy must remain the same or increase, as in spite of increased excretion in the urine at the end of pregnancy there is no change in its content in the blood. The hypophyseal hormone is probably directly concerned with the growth of the fetus. The regulation of the amounts of hormones seems to be a function of the placenta; in fact, it is most probable that the placenta takes on the function of producing a substance identical with the ovarian hormones and through the fetal portion of the placenta stimulates the anterior lobe of the hypophysis to increased activity.

The influence of the oestrus cycle on the basal metabolism of the rat (Der Einfluss des Ovarialzyklus auf den Grundstoffwechsel der Ratte). Szarka, A., Arch. f. d. ges. Physiol. **222**: 690. 1929.

The results of the investigation are, that in the female rat during prooestrum and oestrum the basal metabolism is about 25% higher than in the metoestrum and dioestrum. The basal metabolism parallels the rhythm of the cycle changes in the ovaries. The highest values of the metabolism lie in the same range as that for male rats, that is, on the average of 7 animals 798.5 Cal. per 24 hours per day per square meter of body surface.—M. O. L.

The influence of the hypophysis upon the metabolism (Zur Frage der Bedeutung der Hypophyse für den Stoffwechsel). Bernhardt, H., Klin. Wchnschr. **9**: 399. 1930.

Good preparations of the anterior lobe of the pituitary gland (especially "praphyson") were studied as to their effect on the standard metabolism in normal and sick people. It was shown that 3-6 tablets of praphyson given daily orally for 2-3 weeks had no distinct effect in two-thirds of the normal persons but caused a decrease of standard metabolism in the rest. Obese patients with high basal rates and low specific dynamic action of food showed a decrease of their basal rates in most cases (80%) and very often a distinct increase in the specific-dynamic effect. Also in patients with exophthalmic goiter a marked tendency of the basal rate to decrease could be stated in many instances. But on the other side patients with Simmonds' disease (Cachexia hypophyseopriva) showed a distinct rise in their basal rates and specific dynamic action of food after a medication with praphyson of 3-4 weeks. The effect of the pituitary preparation is very slow compared with thyroid preparations but has a tendency to last for some time. It can be stated that the extracts of the anterior lobe seem to have a tendency to regulate the metabolism always in the direction towards the normal state, a very interesting fact different to all other extracts we know. A short description of three cases of a typical Simmonds' disease is added; these cases were sent to the clinic as exophthalmic goiter but they showed a low basal rate that led to an exact analysis of the endocrine system. Marked disturbances of the pituitary system could be stated. One subject showed a tumor of the hypophysis and could be bettered by x-ray treatment, another developed later on a severe case of osteitis fibrosa. She died in extreme emaciation (28 kgm.), in necropsy a tumor of the parathyroids was found (Recklinghausen's disease), but nearly all endocrine glands were altered.—Author's Abst.

Protein metabolism and fasting hypophysectomized dogs (Metabolismo nitrogenado de los perros hipofisoprivos en el ayuno). Braier, B., Rev. Soc. argent. de biol. **7**: 140. 1931.

Hypophysectomised dogs on ample diet have a normal nitrogen excretion. Creatinin is somewhat reduced (9-18%). Fasting hypophysectomised dogs eliminate from 30 to 35% less N and creatinin than the controls, their blood sugar falls markedly and they often have hypoglycemic convulsions that if not treated by glucose injection may cause death. Dogs with extensive lesion of the tuber behave as normal animals.—J. T. Lewis.

Nitrogenous metabolism in specific dynamic action of hypophysectomized dogs (Metabolismo nitrogenado en la acción especifica dinámica de los perros hipofisoprivos). Braier, B., Rev. Soc. argent. de biol. **7**: 254. 1931.

Submitted to the same meat diet normal and hypophysectomised dogs eliminate the same amount of urinary N per kgm. body weight. During fasting operated dogs eliminated one-third less N than the controls. After ingestion of meat operated dogs had a smaller elevation in the urinary N excretion during 6-8 hours than that observed in normal controls, the increase being more marked in the subsequent period (16-18 hours). So that the total for 24 hours is the same in both groups, the operated animals having a lag with respect to normal ones. Dogs with lesions in the infundibulum behaved as the normal controls. The essential difference found in hypophysectomised animals is a slower elimination of N after ingestion of meat.—J. T. Lewis.

Influence of bacillus coli vaccine on nitrogen metabolism of hypophysectomized dogs (Influencia de la vacuna Coli sobre el metabolismo nitrogenado de los perros hipofisoprivos). Braier, B., Rev. Soc. argent. de biol. **7**: 305. 1931.

Hyperthermia after injection of vaccine is the same in fasting operated animals and in controls. Urinary N increases more in controls.—J. T. Lewis.

Protein minimum in hypophysectomised dogs (Mínimo proteico en la insuficiencia hipofisaria). Braier, B., Rev. Soc. argent. de biol. **7**: 340. 1931.

After 4 days of protein fast the protein minimum was 42% lower in operated dogs than in controls. With complete diets the difference is 34%. During complete fast operated dogs eliminate 30% less nitrogen than controls. Urinary creatinin is 35% less. On a meat diet urinary creatin is 24% lower, and on protein free diets 39% lower.—J. T. Lewis.

Phlorizin action in hypophysectomized toads (Acción de la floridcina sobre los sapos hipofisoprivos). Di Benedetto, E., Rev. Soc. argent. de biol. **7**: 196. 1931.

After extirpation of the pituitary, or even of the anterior lobe, phlorizin usually does not produce glycosuria. It produces hypoglycemia, convulsions and high mortality. Lesions of the infundibulum produce a slight decrease in the effects of phlorizin due to inhibition of the pituitary. Implantation of anterior lobe in operated animals restores the usual effect of phlorizin. There is glycosuria and the blood sugar has values approximating those of normal phlorizinized animals.—J. T. Lewis.

Observations on metabolism of healthy children with a consideration of the specific dynamic action of food (Untersuchungen uber den Gasstoffwechsel gesunder Kinder mit Berucksichtigung der specifisch-dynamischen Wirkung der Nahrung). de Bruin, M., Jahrb. f. Kinderh. **132**: 257. 1931.

The specific dynamic action is considered by R. Plaut, Knissing, Kestner and others to be a function of the hypophysis which is reduced in hypopituitarism, especially of the anterior part. It is determined by taking the difference in the basal metabolic rate taken two to three hours after a protein meal and the fasting initial basal rate expressed in percentage. In adults, the postprandial figure should be 20 to 40 above the first. The author studied the specific dynamic action in 95 children in the Netherlands between the ages of 4 and 10 years using the Dusser de Barenne and Burger apparatus and the following method: (1) Rest for 30 minutes. (2) Three basal metabolic rates taken after fast. (3) Protein breakfast of one-third liter of milk. (4) Rest of three-quarters of an hour. (5) Four basal determinations made, the last to be taken three hours after the meal. He concludes that the basal metabolic rate in children of this age group in the Netherlands is higher than that of American children. It is difficult to judge the significance of the specific dynamic action as this showed such great excursions not only between different children of the same age but also in the same child on different days. Age had no influence.—M. B. C.

Animal calorimetry. The specific dynamic action of meat in hypophysectomized dogs. Gaebler, O. H., J. Biol. Chem. **81**: 41. 1929.

No marked change in specific dynamic action of protein was observed in a dog after removal of the pituitary. The basal respiratory quotients of the animal did not indicate any change in oxidation of carbohydrate. The height of specific dynamic action at a variable time after protein ingestion bears no quantitative relationship to the concentration of the amino acids which are circulatory in the blood.—Author's Summary.

Calcium and phosphorus in plasma of hypophysectomized dogs (Calcio y fósforo del plasma sanguineo de los perros hipofisoprivos). Gerschmann, R., Rev. Soc. argent de biol. **7**: 302. 1931.

Normal values were found in eight cases examined.—J. T. Lewis.

Experimental studies of the anterior pituitary. II. The occurrence of pregnancy cells in mice following continuous anterior-lobe administration. Haterius, H. O. and H. A. Charipper, Anat. Rec. **51**: (No. 1). 1931.

Normal non-pregnant mice were given nine daily implants of fresh anterior-lobe material (rat), following which the ovaries and pituitaries were sectioned and compared with the corresponding glands of pregnant animals. The ovaries were decidedly luteal, giving a histological picture similar to that of ovaries of pregnancy. The anterior pituitaries contained typical cells of pregnancy: large ovoid cells containing a vesicular nucleus eccentrically located in a mass of homogeneous cytoplasm which stained deeply with eosin. Control pituitaries, from castrate females receiving pituitary implants and from normal females receiving control tissue implants, were negative in this respect. In a series of males consisting of (1) non-castrate males, (2) castrate males, and (3) castrate, ovarian-implanted males, and receiving treatment similar to that employed in the female series, it was found that the pituitary did not respond to anterior-lobe administration unless ovarian tissue was present in the form of functional grafts. In the ovarian-implanted males subjected to nine days' continuous pituitary treatment the grafts became highly luteal and the pituitaries resembled exactly those of pregnancy. Under experimental conditions, therefore, luteal tissue is essential for the development of a pregnancy cell type in the anterior lobe of the hypophysis. Moreover, there is no sex specificity in so far as the reaction of the pituitary to ovarian influence is concerned.—Authors' Abst.

Relation between the anterior pituitary body and the gonads. III. Fractionation and dilution of ovary-stimulating extracts. Hill, M. and A. S. Parkes, Proc. Roy. Soc., London, **107**: 455. 1931. Abst., Chem. Abst. **25**: 2765.

Two types of reaction, (a) follicular luteinization and formation of atretic corpora lutea without ovulation, and (b) normal follicular maturation and ovulation, were produced in mice, rats, rabbits and ferrets by saline suspensions of pituitary tissue, alkaline extracts of the anterior lobe of ox pituitary, and extracts prepared from the urine of pregnancy. Extensive dilutions experiments with the urine extracts indicated that the two reactions could not be ascribed to the activity of a single hormone producing different responses at different concentrations. Some evidence of separation of the luteinizing and the maturing activity was obtained by alcohol fractionation of urine extracts. Material solution in 50% alcohol was predominatingly luteinizing; that solution in 30% alcohol mainly produced follicular maturation.

Effects of posterior pituitary extracts on basal metabolism. Himwich, H. E. and F. W. Haynes, Am. J. Physiol. **96**: 640. 1931.

In 64 experiments on 20 rats the changes in oxygen consumption, carbon dioxide production and respiratory quotient after the subcutaneous injection of pituitrin, pitressin, and pitocin, were determined by Haldane's method. It was observed that pituitrin decreases the metabolic rate. This action of pituitrin is due to pitressin and occurs despite the effect of pitocin, since pitressin markedly diminishes the metabolic rate, while pitocin increases it slightly, but definitely. Such opposing actions may explain some of the inconsistencies in

the literature since the different preparations used by various observers may have contained varying amounts of the oxytocic and pressor principles. Moreover, some of the previous workers injected pituitrin peripherally in doses that were too small to produce definite changes, since in the present experiments effects on metabolic rate were observed only with large doses.
—Authors' Summary.

Relation of anterior lobe of the hypophysis to cancer of the uterus (Über Beziehungen des Hypophysenvorderlappens Zum Uterus carcinom). Preliminary report. Second communication. Hofbauer, J., Klin. Wchnschr. **9**: 2108. Ibid. 2136. 1930.

In a previous article by the author on the stimulating influence of the anterior pituitary upon the squamous epithelium of the cervix uteri, the results obtained in guinea-pigs after repeated intraperitoneal administration of extracts or intramuscular transplantations of bits of anterior lobe of the beef were published. It was shown that an overgrowth of the squamous epithelium covering the vaginal portion of the uterus can be initiated. In pursuance of such experiments the stimulating influence upon the cylindrical cervical epithelium by the above means could also be demonstrated. Of much interest was the fact that in discreet places a stratified epithelium had replaced the single row of the original cylindric epithelium. Cervices of pregnant women in the various months of gestation were carefully studied. In about one-fourth of the cases examined a peculiar deviation from the normal character of cervical epithelium was found, in that in lieu of one layer of surface or gland epithelium in discreet places a formation of cuboidal or flat epithelial cells, arranged in four to six layers, had occurred. Those nearly formed cell-nests dipped deeply down into the underlying connective-tissue spaces. Occasionally, mitotic figures were seen. With these new experimental and histological facts pointing to a hitherto unknown response of cervical epithelium to a hyperactivity of the anterior pituitary, two other recent developments may be correlated. Zondek showed that in 82 out of 100 cases of carcinoma of the cervix uteri examined the "pregnancy test in urine" was positive. The recent report of the Frauen Clinic in Munich showed that the addition to the local radium treatment of cervical cancer, of radiation of the hypophysis during the last seven years has decidedly increased the number of cures in end-results obtained after five year observation. This new procedure was introduced in this service by the author in 1922.—Author's Abst.

Hypophysectomy and pancreatic diabetes in toads (Hypophysectomie et diabète pancréatique chez le Crapaud). Houssay, B. A. and A. Biasotti, Compt. rend. Soc. de biol. **104**: 407. 1930.

Removal of the pancreas is followed by an intense diabetes in toads. Preceding removal of the entire hypophysis or its anterior part, or injury to the infundibulum, prevents or delays this diabetes. Implantation of the anterior portion of the hypophysis causes reappearance of the diabetes. Grafts of the neural lobe give a similar but less marked result.—J. C. D.

Implantation of pituitary and hyperfeminization of guinea pigs with ovarian graft (Implantación de hipófisis e hiperfeminización de los cobayos con injerto ovárico). Houssay, B. A., L. Giusti and J. M. Lazcano-González, Rev. Soc. argent. de biol. **7**: 103. 1931.

Homologous pituitary implantation in normal and castrated guinea pigs is favorable to the development of a grafted ovary and to its stimulating action on the mammary gland. The ovarian graft (intrarenal) always had a great number of fully developed follicles but no corpora lutea, both in normal and castrate male guinea pigs; hemorrhagic follicles and corpora lutea were sometimes found in castrates who had received pituitary.—J. T. Lewis.

Pituitary and Bidder's organ (Hipófisis y cuerpo de Bidder). Houssay, B. A. and J. M. Lazcano-González, Rev. Soc. argent. de biol. **7**: 248. 1931.

Bidder's organ develops after castration in otherwise normal toads. It does not hypertrophy after castration in hypophysectomised animals. Implantation of glandular lobe of pituitary produces hypertrophy in normal and castrated toads.—J. T. Lewis.

Hemoglobin and red blood cells of hypophysectomized dogs (Hemoglobina y glóbulos rojos en los perros hipofisoprivos). Houssay, B. A., M. Royer and O. Orias, Rev. Soc. argent. de biol. **7**: 314. 1931.

Hypophysectomized dogs have 5% less hemoglobin than controls and the red cell count is lower. The Hb: cell volume ratio is normal.—J. T. Lewis.

Pituitary anterior lobe powder and ovary (Hypophysenvorderlappenpulver und Ovarium; die quantitative Auswertung der Wirkung). Janssen, S. and A. Loeser, Arch. f. exper. Path. u. Pharmakol. **151**: 188. 1930.

Studies were made on anterior lobe powder made by drying to one-sixth of the original weight, administering the powder to infantile female rats intraperitoneally, and examining the ovaries one hundred hours after injection. Groups of ten rats each were treated with increasing amounts of anterior lobe powder which caused an increase of the percentage of positive reactions among the animals. Ten per cent of the rats reacted to 10 mgm. of the powder, 33% to 15 mgm., 50% to 20 mgm. 55% to 25 mgm., 77% to 30 mgm., 80% to 40, 50 and 70 mgm. The authors suggest establishing a procedure of standardization on this basis. It has been stated by means of this procedure that dry anterior lobe powder which had been dried in acetone and kept above phosphorus pentoxide is almost as effective as fresh transplanted glandular tissue.—W. Raab.

The locally limited action of hormones, particularly that of pituitrin, upon the water exchange (Über örtlich beschränkte Wirkung von Hormonen, speziell des Pituitrins auf den Wasserwechsel). Kiss, A., Klin. Wchnschr. **10**: 162. 1931. Abst., Chem. Absts. **25**: 2193.

Pituitrin has an effect upon the connective tissue of the skin, causing an increased water absorption. The degree of its effect depends upon the conditions of the skin, which is apparently under the control of the liver.

The inhibitory action of "Prolan" (pituitary anterior lobe hormone) (Die hemmende Wirkung des Prolan). Martin, E., Deutsche med. Wchnschr. **56**: 580. 1930.

Injection of large amounts of Prolan inhibits menstruation in women and was applied successfully in hypermenorrhoic patients (no effect below 1000 units, optimal effect with about 2000 units).—W. Raab.

Some results with the use of the silver impregnation method in studying the hypophysis (Quelques résultats de l'application de l'imprégnation argentique a l'étude de l'hypophyse). Morato, M. J. X., Compt. rend. Soc. de biol. **105**: 156. 1930.

The glands of two adult cats were treated by the silver nitrate method of Cajal. Three types of cell were seen in the anterior lobe and these are described.—J. C. D.

The action of hypertensive and oxytocic substances from the posterior lobe of the hypophysis on the fat in the blood (Action des substances rétropituitaires, hypertensive et ocytocique, sur les graisses du sang). Nitzescu, I. I. and G. Benetato, Compt. rend. Soc. de biol. **105**. 67. 1930.

Intravenous injections in dogs are followed by a reduction in fat and fatty acid in the blood, whether oxytocin, vasopressin, or pituitrin is used.—J. C. D.

Studies of the effects of serum from acromegalics on the growth of young animals (Recherches sur l'action du sérum d'acromégalique sur la croissance des jeunes animaux). Parhon, C. I., L. Ballif and A. Stirbu, Compt. rend. Soc. de biol. **104**: 227. 1930.

Small doses of blood serum from a woman with active acromegaly were injected daily into two young guinea pigs and serum from a normal person into three controls. Three and a half months later, one control had gained more and one less than the experimental animals.—J. C. D.

An hereditary anterior-pituitary deficiency in the mouse. Smith, P E. and E. C. MacDowell, Anat. Rec. **46**: 249. 1930.

A preliminary report is given upon the disabilities in hereditary dwarfism appearing in a strain of silver mice being reared by MacDowell at Cold Spring Harbor. The dwarfism appears abruptly at about the fifteenth day of life. The dwarfs remain sterile. Thyroids, adrenals and reproductive organs exhibit, in a lesser degree, the same structural abnormalities as described by one of us in hypophysectomized rats. The posterior lobe of the pituitary appears to be normal; the anterior lobe contains no typical eosinophiles and is largely composed of connective tissue. No definite conclusions have been drawn regarding the presence or absence of basophiles. Chromophobes, though possibly present, are greatly reduced in number. Daily anterior-pituitary implants have been given to six dwarfs. These induced a normal rate of general body growth, although the great difference in size between the dwarfs and normals at the beginning of treatment has not been entirely overcome. The implants induce growth of the reproductive organs and bring the thyroids and adrenals to a normal condition. Thirty young sired by a treated dwarf male have been born. The anterior pituitary alone, of the endocrine glands, is not repaired. It is concluded that dwarfism and associated abnormalities appearing in this strain of mice are due to a deficiency of the anterior pituitary, which is inherited in an alternative manner.—Authors' Abstract.

Temperature and thermal reactions of hypophysectomized dogs (Temperatura y reacciones térmicas de los perros hipofisoprivos). Solari, L. A., Rev. Soc. argent. de biol. **7**: 216. 1931.

A lowered temperature is an inconstant symptom in hypophysectomized dogs, occurring only in 10% of cases. Temperature reactions to tetrahydronaphthilamine, Bacillus coli vaccine and fasting is identical in normal and operated dogs. Sharp rises and falls in temperature are observed in some hypophysectomized dogs and in others with only lesions of the infundibulum; they are apparently due to the alterations in the nervous centers.—J. T. Lewis.

Anterior lobe of the hypophysis and rupture of the follicle in rabbits (Lobe antérieur de l'hypophyse et rupture folliculaire chez la Lapine). Stricker, P. and F. Grueter, Compt. rend. Soc. de biol. **104**: 394. 1930.

Rupture of the follicle normally does not occur spontaneously in rabbits. Injections of anterior lobe were given to six rabbits in heat. Rupture had occurred in all animals examined seventeen or more hours after the injection.
—J. C. D.

Decreased absorption from the alimentary tract following injection of posterior pituitary extract. Thienes, C. H. and A. J. Hockett, J. Lab. & Clin. Med. **16**: 843. 1931.

Subcutaneous injection of reliable commercial extracts of the posterior lobe of the hypophysis resulted in a decrease in the rate of absorption of strychnine sulphate, morphine sulphate, cannabis, potassium iodide and glucose from the gastrointestinal tract. There was a delay of onset and decrease in symptoms produced by strychnine sulphate administered by stomach tube to rabbits, and by morphine sulphate (stomach tube) and fluid extract of cannabis (soft capsule) in dogs. Pituitary solution failed to alter the response of dogs to morphine sulphate administered subcutaneously. Decreased urinary and salivary excretion of orally administered iodide in man and rabbits was found. There was a decrease in the rise of blood sugar from orally administered glucose in rabbits and an increase in the amount of glucose and of iodide remaining in the gastrointestinal tract of rats two hours after administration of the respective substances by stomach tube.—M. O. L.

Pituitary (posterior lobe) extract and insulin (Über die antagonistischen Beziehungen zwischen Hinterlappenhormonen und Insulin). Velhagen, K., Arch. f. exper. Path. u. Pharmokol. **142**: 127. 1929. Abst., Physiol. Absts. **16**: 58.

A series of experiments on rabbits is described, in which extracts of fresh pituitary glands of cattle were injected. It was shown that the principle in the posterior lobe which raises blood sugar and antagonizes insulin occurs both in the pars neuralis and in the pars intermedia. In order to prevent the oc-

currence of hypoglycaemia very large doses of posterior lobe had to be given. Thirty-five units of insulin produced hypoglycaemia after 900 mgm. of pars neuralis had been injected. Repeated injections of posterior lobe extract could not inhibit the action of circulating insulin, and diabetes mellitus did not result. The secondary hypoglycaemia, which often occurs after administration of posterior lobe extracts, is probably due to an increased secretion of insulin, as it does not occur in animals in whom the pancreas has been destroyed. Insulin does not antagonize the action of the posterior lobe on the blood pressure and on the uterus.

The action of insulin on the perfused frog heart and on the isolated rabbit intestine. Barlow, O. W., J. Pharmacol. & Exper. Therap. **41**: 217. 1931.

The effects of various concentrations of insulin on the sympathetic and parasympathetic nerve endings were noted by means of the perfused intact frog heart and Magnus preparations of isolated rabbit intestine. Moderate concentrations of insulin produce a significant improvement in the rats, amplitude of contraction and tonus of the perfused heart. High concentrations are paralytic to the muscle. During the insulin stimulation, the cardiac response to inhibitory (vagus) stimulation was diminished. The stimulant effects of insulin occur during maximal accelerator (electric) nerve stimulation, so that the stimulant action is at least partly muscular. However, the degree of response indicates that in addition to the muscular action a peripheral stimulation of the sympathetic mechanism occurs. This possibility was rendered more plausible by the divergent reaction of the reused intestine under similar conditions. The intestine reaction to insulin is shown by a brief depression followed by a more lasting stimulation. The depression resembles that of epinephrine, involves mainly the tone and does not occur after ergotoxins. The augmentation appears to be muscular analogous to the cardiac reaction. Atropine does not materially affect the phenomena in either the heart or the intestine, so that these do not involve parasympathetic stimulating.

—Author's Abst.

The appearance of diabetes mellitus after acute pancreatic disease (Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen). Bernard, F., Klin. Wchnschr. **10**: 632. 1931.

Of the 50 cases operated for pancreatic disorders, three have died of diabetes and two are receiving treatment for this disorder. The carbohydrate tolerance test (glucose tolerance) in 25 of these cases showed that five of them had a latent disturbance of sugar metabolism. In operations for pancreatic necrosis, the simultaneous removal of the gall bladder did not prevent the development of diabetes. As a preventive measure the author recommends careful postoperative treatment in all patients in whom there is a hypofunctioning of the islet tissue of the pancreas. The author believes that impairment of the pancreas by necrosis makes patients prone to diabetes and suggests frequent carbohydrate tolerance tests in order to detect early manifestations of a lowered carbohydrate metabolism.—E. L.

The action of insulin on the muscle contraction of the frog (L'azione dell'insulina sulla contrazione mus). Bucciardi, G. and A. De Niederhäusern, Boll. d. Soc. ital. di biol. sper. **5**: 870. 1930. Abst. Chem. Absts. **25**: 2198.

Insulin injected into the frog causes an increase in the amplitude of muscle contractions and muscular work. The increase in the capacity for work coincides with a diminution of muscular glycogen. Insulin convulsions cause a diminution of muscle glycogen and a decrease in muscular work.

Effect of insulin on the appearance of the sexual cycle in white rats (Action de l'insuline sur l'apparition des cycles sexuals chez le Rat blanc). del Castillo, E. B. and C. Cardini, Compt. rend. Soc. de biol. **105**: 117. 1930.

Four lots of six young rats each, four experimental and two controls were injected daily with 0.1 unit of highly purified insulin. There was no difference between the experimental and control animals in the age at which the vagina opened or the first oestrous occurred.—J. C. D.

Insulinemia in obesity and in emaciation (L'insulinemia nell'obesite e nella magrezza). Columba, D., Policlinico, **38**: 219. 1931. Abst., J. A. M. A. **96**: 1837.

Columba studied insulinemia on 12 obese and 10 underweight persons. From 30 cc. of venous blood taken from the hollow of the elbow, he extracted, by the acetone-trinitrophenol method, a substance having the action of insulin, which, when injected into a rabbit that has fasted for 18 hours, induces at first a hyperglycemic reaction and later a hypoglycemia reaction. The hypoglycemic potency of the extract obtained from the blood of the obese was in every case less than that of the extract derived from the persons who were underweight. He concludes that there is in the obese a state of hypo-insulinemia, which is to be regarded as the expression of a latent state of functional insufficiency of the pancreas.

The response of sympathectomized animals to insulin. Dworkin, S., Am. J. Physiol. **98**: 467. 1931.

Bilateral extirpation of the sympathetic nerve chains renders cats permanently hypersensitive to injected insulin. Even after small doses all the signs of hypoglycemia quickly supervene; these include polypnea, salivation, relaxation of sphincters, and strong tonic convulsions. The blood-sugar curves after insulin show a rapid and precipitous decline, with no evidence of spontaneous recovery. Restitution to normal can be effected by injection of small amounts of epinephrin or of glucose. Inasmuch as these animals never develop hypoglycemic symptoms under natural conditions, it is inferred that the physiological insulin secretion in these cats is always at a minimum, both in rate and quantity. In some instances after intravenous injection there is a brief initial hyperglycemia; its significance is unknown—Author's Summary.

Hypoglycemia; the clinical syndrome, etiology and treatment; report of a case due to hyperinsulinism. Gammon, G. D. and W. C. Tenery, Arch. Int. Med. **47**: 829. 1931.

Hypoglycemia may result from several types of abnormal mechanisms: (1) from disturbance of carbohydrate control (a) through overproduction of insulin by hyperfunction, hypertrophy or tumor of the islets or (b) through loss of the substances that are antagonistic to insulin as in hypo-adrenalinism, hypothyroidism, pituitary dysfunction or combinations of these; (2) from interference with storage or release of glycogen in the depots of the body—the liver and muscles—or from depletion of glycogen from physical effects; (3) from conditions in which dextrose is lost from the body as such, e.g., in renal diabetes, or as other sugar, e.g., in lactation. The most important cause, by far, is that of overproduction of insulin. In attempting to distinguish the various types of hypoglycemia, one must look for concomitant evidence of disorders of the endocrine glands or glycogen depots or of the loss of carbohydrate. Hypoglycemia of pancreatic origin presents a typical syndrome recognized without difficulty. The point of distinction between hypoglycemia seizures and other convulsive states rests on the depressed blood sugar level. A history of relief from the ingestion of food often suggests this investigation. A review of the clinical manifestations of pancreatic hypoglycemia has been attempted, based on the cases reported in the literature. A typical case of hyperinsulinism has been added to this group. In order to contrast pancreatic with other forms of hypoglycemia, examples of the various types of spontaneously appearing hypoglycemia have been cited. Outlines of the details of the available reports of pancreatic hypoglycemia and of the leading causes of the other types are given.
—Author's Summary.

Some questions and problems of diabetes research including some evidence of a metabolic-physiological theory of diabetes mellitus. Geelmuyden, H. C., Ergebn. d. Physiol. **31**: 1. 1931. Abst., Chem. Abst. **25**: 3061.

Insulin has no direct influence upon the oxidation of carbohydrates in the animal body. It fails to increase the total heat production and metabolism in the animal body. It can accelerate carbohydrate oxidation by providing intermediary compounds whose existence conditions carbohydrate oxidation such as muscle work (hypoglycemic convulsions), fat and glycogen synthesis. Furthermore, insulin can promote counter reactions of the nervous-endocrine metabolic

regulation by which the total oxidation and thereby that of carbohydrates can be accelerated positively or decreased. Such considerations probably explain the diverse findings of various authors in their studies of the effect of O_2 intake upon insulin. The basic reaction of insulin appears to produce a decrease in the formation of carbohydrates from non-carbohydrate materials; this in turn forces the body to burn preformed carbohydrates. This results in an increased R.Q. and a decreased O_2 intake. This basic type of insulin reaction is in accord with the conception of diabetes mellitus as a pathological acceleration of sugar formation from non-carbohydrate materials.

The action of insulin on thermoregulation (Azione dell'insulina sulla termoregolazione). Ceruti, G. and E. Sapegno, Boll. d. Soc. ital. di biol. sper. **5**: 905. 1930. Abst., Chem. Abst. **25**: 2198.

Under the action of insulin, if the dose has been insufficient or due to the peculiar condition of resistance of the individual animal the hypoglucemia does not reach below a certain level, the internal temperature does not vary markedly. However, if the dose has been sufficiently large to produce a marked lowering of blood sugar approaching the convulsive dose (0.06-0.05%) then there is a rapid fall of temperature which is related to the glucemic titer. The fall of temperature is arrested by the injection of glucose. The temperature was determined by a thermocouple method.

Studies in carbohydrate metabolism. II. Glucose-lactic acid cycle in diabetes. Himwich, H. E., W. H. Chambers, Y. D. Koskoff and L. H. Nahum, J. Biol. Chem. **90**: 417. 1931.

Twenty-two observations have been made on nine depancreatized dogs, and eight observations on five phlorhizinized dogs. They all indicate, especially those on depancreatized dogs, that lactic acid is liberated by muscle and removed chiefly by liver, while glucose is poured out by liver to be absorbed by muscle and other tissues or excreted. Thus the glucose-lactic acid cycle between muscle and liver functions in diabetes just as it does under normal conditions. It is clearly demonstrated that by means of this mechanism, lactic acid, a waste product of muscular activity, is converted into a precursor of the glucose of the blood, accounting in the present experiments for approximately 0.4 of the glucose released by the liver.—Author's Summary.

Diabetic resistance to insulin treatment (Les diabétes insulino-résistants). Labbé, M., Rev. belge sc. méd. **3**: 465. 1931.

In a critical review of the literature of cases of diabetes resistant to insulin treatment, Labbé comes to the conclusion that such a condition may really exist, but that it is rare. He considers that the most of the published reports of such refractoriness are based on error of interpretation and can be explained by poorly managed insulin treatment and dietetic régime. Labbé believes that an incomplete resistance to insulin occurs in certain cases of diabetes associated with disorder of other endocrine glands than the pancreas (adrenals, thyroid, pituitary); in a few other cases of pancreatic diabetes refractory to insulin, no explanations have been possible. In order to determine true cases of insulin resistance, either the complete or incomplete form, and to excluded false cases, the following data should be found: (1) In a case of diabetes placed on a proper and exact régime, insulin does not dimish the glycosuria or the ketosis. (2) In a diabetic under the proper régime excessive doses of insulin must be used in order to stop the glycosuria and acidosis and to maintain nutritional equilibrium. (3) The subcutaneous or intravenous injection of insulin in dosages ordinarily used in hypoglycemic tests does not lower the blood sugar or lower it much less than is usually the case in diabetics.—M. O. L.

Diabetes in the negro race. Leopold, E. J., Ann. Int. Med. **5**: 285. 1931.

Some authors have stated that diabetes mellitus is a rare disease among the colored race. From mortality statistics of the city of Baltimore, the death rate of the negro due to diabetes is slightly higher than that among the white. Diabetes is more common among females of the negro race than among those of the white. The author believes this fact may be due to obesity which is common.—E. L.

The action of insulin on gastric secretion (Über die Wirkung des Insulins auf die Magensekretion). Meyer, P. F., Klin. Wchnschr. **9**: 1578. 1930. Abst., Am. J. M. Sc. **181**: 578.

In view of the contradictory reports of previous investigations, the author undertook a carefully controlled study of the influence of insulin on gastric acidity and secretion in a variety of patients. He finds that in essentially normal individuals a dose of about 8 units of insulin subcutaneously or 6 units intravenously produces a constant increase of gastric acidity of pronounced degree which reaches its maximum in from 75 to 90 minutes. Along with this the majority of patients show an increase in the volume of gastric secretion. This action is shown to be specific for insulin and not due to its protein content. The action is also proved to be an early symptom or an actual side action of the hypoglycemia produced by insulin, there being a strict parallelism between the elevation of gastric acidity and the depression of blood sugar. Patients with diabetes fail to show gastric hyperacidity from insulin unless the dose is sufficient to induce hypoglycemia and in all diabetic patients the gastric effects of insulin are less marked than they are in normal individuals. Insulin is at least as effective as histamin in separating patients with total achylia from those with partial achylia, if not even more effective. From these studies it is evident that insulin is contraindicated as a means of improving nutrition in those patients suffering from hyperacidity, while on the other hand it is specially suitable for those with subacidity and anorexia.

The production of hypoglycemia in rabbits by oral administration of precipitated insulin. Mukherjee, H. N., J. Physiol. **70**: 182. 1930. Abst., Chem. Absts. **25**: 3083.

The phosphotungstic acid precipitate of crude insulin, administered to fasting rabbits by mouth, lowered blood sugar to the convulsion level within one to two hours. Beneficial effects have been noted with diabetic patients after its administration. It appears to have no toxic effects.

Insulin angina. Parsonnet, A. E. and A. S. Hyman, Ann. Int. Med. **4**: 1247. 1931.

In the authors' 89 cases of coronary thrombosis, 22 of the patients had definite diabetic symptoms. Of this group, 7 had severe coronary seizures following administration of the initial dose of insulin. Four of the case histories are included in this report. The authors believe that lowering of blood sugar following insulin therapy in a heart adjusted to a high blood sugar causes the symptoms. Lowering of blood sugar in any of the cases did not approach the values necessary for hypoglycemic shock. In 4 cases the stenocardial effect was sufficient to alter the electrocardiographic tracing, but in 3 cases there were no alterations in the electrocardiogram. The authors feel that in arteriosclerosis the heart should be carefully examined before insulin therapy is instituted and that insulin therapy should not be resorted to in cardiovascular disease unless dietary measures have failed.—E. L.

The insulin-sensitivity of non-diabetic humans and its relationship to the vegatative nervous system (Die Insulinempfindlichkeit des nichtdiabetischen Menschen und ihre Beziehung zum vegetativen Nervensystem). Stamm, E., Arch. f. Verdauungshr. **48**: 104. 1930. Abst., Chem. Absts. **25**: 2192.

The intravenous injection of 1/15 unit of insulin into normal subjects causes a maximal fall in blood sugar of 66.50%. In vagotonic subjects, this may be as high as 45.6 mgm. %; in hyperthyroidism it averages 47.2 mgm. %. On the other hand, in subjects with increased sympathetic tone (e.g., with hyperthyroidism) there is less sensitivity to insulin with an average fall of only 16.9 mgm. % under the same conditions.

Basal metabolism in diabetic children. Topper, A., Am. J. Dis. Child. **42**: 760. 1931.

This report is based on a study of 100 basal metabolic rates made on 27 diabetic children under treatment with insulin. Determinations were made over periods of one to four years of age at six-month intervals. The rate in treated diabetic children is essentially normal. There is an increase in the basal metabolic rates between 15 and 17 years of age which is probably a

manifestation of puberty. This occurs normally in children between 11 and 14 years of age but as puberty seems to be delayed somewhat in diabetic children as evidenced by late appearance of menstruation, the prepuberty rise in metabolism is also delayed. The results obtained agree with those of Joslin and White. Beck has found that the basal metabolic rate is normal with insulin and with a normal or low excretion of sugar in urine. There is an increased rate without insulin and with a high urinary sugar excretion.—M. B. G.

Adenoma of the islands of Langerhans with hypoglycemia: Successful operative removal. Womack, N. A., W. B. Gnagi and E. A. Graham, J. A. M. A. **97:** 831. 1931. Abst., A. M. A.

The authors report the case of a patient with hypoglycemic seizures due to an adenoma of the islands of Langerhans. The tumor was removed with a complete relief from symptoms. The mechanism of the production of the apparent hyperinsulinemia was obscure. Microscopic examination showed that while many of the cells were abnormal morphologically and some of the secretory antecedents were unusual in type, ordinary beta granules were plentiful. Furthermore, the clinical picture and the reaction of the patient to dextrose when administered were of the type encountered in the reaction of the body to an overdosage of insulin. Therefore, while it is possible that in such a case as this dysinsulinemia is present, there is no proof that the product is not a normal secretory one. When one considers the excessive amount of insulin-producing tissue that exists in the body, the remarkable feature is that hyperinsulinemia is not more common. In several cases in which the cause of the phenomenon was not apparent, partial resection of the pancreas was done. The results on the whole have been unsatisfactory. The work of Allen on dogs has shown that in this animal roughly about nine-tenths of the pancreas must be removed before there is a constant production of glycosuria. If the same relationship holds in man, such a procedure to be efficient would be technically very difficult. If such a tumor as the one described by the authors should occur in the head of the pancreas or in the substance of the body, it would be extremely difficult to discover at operation. For this reason they feel that such a picture of hypoglycemia as they have described should not be considered idiopathic in origin until careful section of the pancreas is made at necropsy. At postmortem examination such a growth is probably often missed unless special care is taken.

Sugar formation from phosphatids (Sobre la formación de azúcar a expensas de los fosfatides). Yriart, M., Rev. Soc. argent. de biol. **7:** 203. 1931.

In dogs made diabetic through pancreatectomy or injection of phlorizin, injection of lecithin does not increase the production and excretion of glucose, contrarily to what Jost has observed in the liver perfused with phlorizin.
—J. T. Lewis.

Studies on the chemistry and the physiology of the parathyroid hormone. Allardyce, W. J., Am. J. Physiol. **98:** 417. 1931.

Cats have been found to show little or no rise in serum calcium within the first two hours after injecting parathyroid hormone intravenously, even when as much as one hundred units were given, and hence cannot be used, as suggested by Stewart and Percival, in assaying extracts of the parathyroid hormone. The potency of the active principle obtained by acid hydrolysis was not altered by making the hydrolysate alkaline to phenolphthalein. Acid hydrolysis freed the active principle of the parathyroid glands, but too long hydrolysis destroyed it. Using 1.5, 3 and 5% hydrochloric acid, the rate of destruction increased with the strength of acid used. With these strengths of hydrochloric acid, the most potent extract was obtained by hydrolyzing for 45 minutes with 1.5% acid. The parathyroid glands exhibited a marked buffering action. In the course of preparing active extracts, heating at 80° to 100° was found necessary in order both to free the active principle and to destroy enzymes which would otherwise inactivate the hormone. Acid was also found essential for the freeing of the active principle from the glands. Saponin, applied as in Harington's method for purifying insulin, did not separate active and inactive fractions from "Parathormone," but destroyed all activity originally present. Gradually approaching the isoelectric point from the acid side yielded an amorphous precipitate without a separation into active and inactive

fractions. Saturation of an alkaline solution with carbon dioxide removed all the activity in an amorphous precipitate which came down about pH 6.8. Smaller amounts of carbon dioxide failed to yield an inactive fraction. Continous extraction with absolute ethyl alcohol did not alter the composition of the isoelectric precipitate. Continous extraction, first with absolute normal butyl alcohol, and then with saturated aqueous butyl alcohol, did not alter the composition of the isoelectric precipitate. Addition of potassium acid phthalate to a solution of the active principle did not remove an inactive fraction. Dogs responded better and more uniformly on a meat diet than they did on an oatmeal diet. This uniformity was further improved by the addition of cod-liver oil. Increasing the readily available calcium by feeding calcium lactate did not bring about a more uniform response. Extracts prepared from oatmeal gave no evidence for the presence in the cereal of an interfering or antagonistic factor to the parathyroid hormone. Decrease in response with repeated injections was found to be due to an increased tolerance rather than a depletion of readily available calcium. Intravenous injection of the parathyroid hormone gave the maximum elevation of the serum calcium in four to eight hours and the response was considerably less than when the hormone was given either subcutaneously or intramuscularly.—Author's Summary.

Contributory factors in parathyroid tetany in dogs; high temperature, panting and overventilation. Bryan, W. R. and W. E. Garrey, Am. J. Physiol. **98**: 194. 1931.

Evidence is presented which corroborates the view that, following parathyroidectomy in dogs, there is no appreciable variation in the pH of the blood until tetany actually develops. The body temperature is shown to rise slowly with the development of fibrillary contractions and rapidly after the onset of violent tetanic attacks. In extreme instances the body temperature may reach 44° C. A definite shift, toward alkalinity, i.e., increased pH and decreased carbon dioxide tension, of the blood develops as a result of overventilation due to the panting which accompanies the rise in body temperature during the acute attacks. In parathyroidectomized dogs the existing hyperexcitability due to low blood calcium, is augmented by increased alkalinity due to panting. These summated conditions may precipitate attacks or markedly intensify attacks in progress. An equivalent or even greater acid-base change accompanying a rise in temperature and panting of otherwise normal dogs does not precipitate tetanic attacks. The acid products of muscular activity during a tetanic attack may temporarily overcome the decreased hydrogen ion concentration due to overventilation and may thus cause a temporary decrease in the severity of the attack; this phase is followed by an exacerbation of the attack when the increased pH of overventilation again predominates. The augmentation of parathyroid tetany during the inspiratory phase of respiration is confirmed. The important components in the symptom complex after parathyroidectomy in dogs develop in the following sequence: fibrillary muscular contractions, a rise of body temperature, which in turn causes panting and results in overventilation and increased pH. Violent tetany ensues and further augments the rise of temperature. There is thus instituted a vicious cycle which progressively increases the severity of the attack unless relief is obtained by suppression of one or more of the contributory factors.
—Authors' Summary.

Calcium content of the brain and kidney of animals receiving Collip's parathormone (Sur le teneur en calcium du cerveau et des reins chez les animaux ayant recu des injections de parathormone de Collip). Parhon, C. I. and M. Cahane, Compt. rend. Soc. de biol. **104**: 518. 1930.

Five guinea pigs and two rabbits with controls were injected over periods of from 5 to 36 days. No consistent difference between experimental and control animals could be found.—J. C. D.

Relationship between the parathyroid hormone and the growth of rat carcinoma. Raik, T. S., Tr. Jap. Path. Soc. **21**: 653. 1930. Abst., Chem. Absts. **25**: 3720.

Albino rats and the Flexner-Jobling carcinoma were used. Subcutaneous inoculations were done by the trocar method. Group I received parathormone of Parke-Davis & Co., 0.025 unit per 50 grams body weight once a day. In Group II, both parathyroids were extirpated. In Group III the parathyroid

glands of other healthy albino rats were transplanted into the rats in this group. Group IV rats were injected once daily with 0.2 cc. of 2% $CaCl_2$ solution per 50 grams body weight. All animals received an exclusive diet of barley and water. In Group I the body weight did not show marked changes, whereas the weight of the controls increased regularly and the tumor growth showed marked increase in the test group. In Group II there was no change in body weight, whereas the controls showed increase in body weight. The group of the tumor was very slow for the first 10 days but later increased gradually. In Group III the body weight increased as gradually as the controls and the tumor increased at a fairly rapid rate for 14 days, after which time the growth was parallel to that of the controls. In Group IV the rate of the body was the same as for the controls while the tumor growth was markedly disturbed and diminished or even absent.

Studies on the physiology of glands. CXX. The growth-regulating function of the thymus gland (Beiträge zur Physiologie der Drüsen). Asher, L. and P. Ratti, Biochem. Ztschr. **223**: 100. 1930. Abst., Chem. Absts. **24**: 5362.

Addition of thymus to the usual diet of young rats causes considerable stimulation of growth within normal limits. This stimulating action is exerted even when the animals are kept in the dark. By means of thymus extracts or thymus feeding the rats can be fully protected from development of rickets either on the McCollum diet or in animals kept in the dark. However, the effect of the thymus is not strictly specific as this can be produced also by feeding meat. Hyperthymism results are produced even under conditions of undernutrition or poor hygienic conditions, which is taken as evidence of influence of the thymus on growth.

Effect of diiodotyrosine on the hyperthyroid metabolism (Einfluss des Dijodtyrosins auf den hyperthyreotischen Stoffwechsel). Abelin, I., Biochem. Ztschr. **233**: 483. 1931. Abst., Chem. Absts. **25**: 3727.

It has long been known that diiodotyrosine, diiodotyramine as well as thyroid substance accelerate metamorphosis. Because the former has no effect on metabolism its consideration in the thyroid function mechanism has been neglected. However, it has been shown in recent years that thyroglobulin contains much diiodotyrosine. It is shown that diiodotyrosine does hinder the development of hyperthyroidism (abnormal rise in basal metabolism, extreme perspiration, overexcitability, etc.) or ameliorates toxic symptoms. It is shown by experimental results on rats fed dry thyroid gland that the administration of diiodotyrosine materially reduces the basal metabolism. The liver glycogen does not decrease as rapidly under combined administration of thyroid and diiodotyrosine even when the thyroid dose is such that even combined with sugar feeding it depletes the liver glycogen completely.

Influence of thyroid gland substances on the total creatinine content of liver and muscles (Über den Einfluss der Schilddrüsensubstanzen auf den Gesamtkreatiningehalt der Leber und des Muskels). Abelin, I. and W. Spichtin, Biochem. Ztschr. **228**: 250. 1930. Abst., Chem. Absts **25**: 994.

Feeding rats on thyroid substance causes a great diminution in the total creatinine content of the liver and of the striated muscles. The loss of creatin-creatinine, the almost complete absence of glycogen and strong reduction of the fat depots are all manifestations of the injuries to the hyperthyroid metabolism.

Demonstration of an antiglycogen substance (thyroid hormone) in the blood of pregnant women (Nachweis unter glykogenvermindernden Substanz [Schilddrüsen-hormone] im Blute von Schwangeren). Anselmino, K. J. and F. Hoffmann, Arch. f. Gynäk. **143**: 310. 1930. Abst., Chem. Absts **25**: 3709.

The blood of pregnant women contains a substance which when injected subcutaneously into mice decreases the glycogen content of the liver. It is demonstrable from the second month of pregnancy onward, and increases in concentration during the course of pregnancy. On the second day post partum its concentration decreases and by the eighth day post partum it has completely disappeared. The concentration of this substance is much less in the fetal blood than in the maternal blood. At the end of pregnancy 2.5 cc. of the blood serum from a woman at the end of pregnancy produces a decrease of as much as 75% in the glycogen content of the mouse liver. The substance has

been identified as thyroid hormone. In its action in decreasing the glycogen content of a mouse liver 2.5 cc. of the serum corresponds to 40-50 (r) thyroxin.

Exophthalmic goiter in children. Beilby, G. and J. G. Carlton, New York State J. Med. **31**: 1329. 1931.

The authors encountered five instances of goiter under puberty out of a total of 1600 in all ages. The youngest was 2 years and 9 months old. They feel that exophthalmic goiter in children differs in no way in symptomatology and course from the disease in adults. The thyroid shows the same characteristic enlargement and there is exophthalmos, tachycardia, tremor, hyperactivity, irritability, nervousness, increased appetite and loss of weight. They advise the following procedure for operative cases: (1) A long preoperative period of hospitalization. (2) Preoperative preparation with Lugol's solution. (3) A single operation is more advisable than multiple. (4) It is best not to remove too much gland because of the dangers of hypothyroidism but, on the other hand, the same proportion of gland may be removed as in an adult because of the great regenerative powers of thyroid tissue in a child. Of the five cases reported, three of the children have remained well with no evidence of recurrence within two to nine years, one had a slight recurrence and the fifth was operated on too recently to express an opinion as to the results.—M. B. G.

The iodine metabolism in Basedow's disease and the explanation of the post-operative reaction following thyroidectomy (Der Jodstoffwechsel des Morbus Basedowii sowie die Erkärung des postoperative Reaktion nach Thyreoidektomie). Bier, A., Klin. Wchnschr. **9**: 819. 1930. Abst., Chem. Absts. **25**: 3051.

Following thyroidectomy, there is a 5-10% fall in blood iodine, i.e., the post-operative reaction is not due to the mechanical expression of the thyroid. Instead, it is considered due to a sudden fall of the thyroid secretion, a "hypothyroxic" shock, in an organism on a high level of iodine metabolism; it is best avoided by continued treatment with iodine up to and following thyroidectomy. The author points to the fact that the post-operative urine contains only traces of iodine, indicating insufficiency and retention rather than overdosage.

Physostigmine salicylate in the treatment of exophthalmic goiter. Observations on two hundred cases. Bram, I., Arch. Int. Med. **48**: 126. 1931.

The results of the administration of physostigmine for a period of ten weeks in 200 cases of active exophthalmic goiter are discussed. In 98, or 49%, the benefit obtained was highly encouraging and may be lasting; in 48, or 24%, the benefit was transient though tangible, and in the remaining 54, or 27%, no benefit was discerned. Excepting in five patients suffering from persistent diarrhea, no contraindications or untoward results were noted from the administration of physostigmine salicylate in doses corresponding to 1/30 grain three times a day in adults. The most satisfactory results were noted: (1) in the extremes of age, i.e., in patients under 14 and above 50; (2) in those approaching remission after having had one or more crises; (3) in sufferers from this disease over a period of four or more years, i.e., the chronic or protracted forms of exophthalmic goiter; (4) in those presenting a basal metabolic rate of less than +40%; (5) in those presenting extreme exophthalmos, and (6) in those presenting cardiac arrhythmia, especially auricular fibrillation. The improvement in the behavior of the heart was the first effect noted. A reduction in rate and force of the heart's action was followed by improvement in the basal metabolic rate and all subjective and objective manifestations of the disease. Improvement in exophthalmos in many instances of chronic and stubborn cases was very gratifying. In a few cases of postoperative recurrence with excessive exophthalmos, physostigmine was particularly satisfactory in results. From the observations herein noted it appears that physostigmine deserves high regard in the management of exophthalmic goiter.
—Author's Summary.

Thyroxin and gastric acidity (Thyroxine et chimisme gastrique). Coelho, E. and J. Rocheta, Compt. rend. Soc. de biol. **104**: 426. 1930.

Twenty patients were given thyroxin, 10 subcutaneously and 10 by mouth. There was an increase in gastric acidity in 8 of the former and 3 of the latter.
—J. C. D.

Hyperparathyroidism and similar diseases of bone. Cooley, T. B., Am. J. Dis. Child. **42**: 691. 1931.

A case report is given of osteitis fibrosa cystica in a girl of 11½ years of age with a B.M.R. of plus 23, blood calcium of 13.6 to 15.2 mgm. per 100 cc. and phosphorus of 2.6 to 3.04 mgm. per 100 cc. Removal of a cystic parathyroid gland and a small colloid goiter was followed by a general improvement, a fall in blood colcium to 6.9 mgm. and in phosphorus to 2 mgm. These later rose to 10.8 and 4 mgm., respectively. Slight post-operative tetany was controlled by calcium gluconate and parathormone. The second case was in a girl of 11½ years of age who presented a bone condition which was diagnosed as either echondromatosis or osteitis fibrosa. The B.M.R. was normal, the calcium 11.1 mgm. and the phosphorus 3.6 mgm. Removal of an adenomatous goiter was followed by a remarkable recovery. The parathyroid was normal.—M. B. G.

The parathyroids and decreased blood calcium following fluorine (Parathyroide et hypocalcémie fluorique). Gerschmann, R., Compt. rend. Soc. de biol. **104**: 411. 1930.

In dogs sodium fluoride injected intravenously produces a reduction in blood calcium. In unoperated dogs, return of calcium to the normal level is rapid but in thyroparathyroidectomized animals the depression is permanent. —J. C. D.

Hyperthyroidism and its treatment (L'hyperthyroidisme et son traitement). Gilbert-Dreyfus, Pp. 297, Doin et Cie, Paris. 1930.

From a study of some of the significant literature and an analysis of 143 cases personally analyzed Gilbert-Dreyfus concludes that exophthalmic goiter represents true "hyperthyroidism" and that "toxic adenoma" does not constitute a separate disease entity. He recognizes a "parabasedowian syndrome" that is purely of autonomic nervous origin but that can simulate exophthalmic goiter. Its prognosis is always benign. Diminished weight is the most reliable sign of exophthalmic goiter, it uniformly showing negative correlation with the basal metabolic rate. Tachycardia is rarely lacking though it does not always correlate closely with the weight and basal metabolic rate changes. Arterial hypertension is not constant. Goiter is also an inconstant sign as are the eye-signs; vasomotor, secretory and psycho-nervous abnormalities are recognized in about 90% of the cases; digestive disturbances in 40-50%. Diminished menstrual flow is the outstanding genital manifestation. Hyperactivity of the sympathetic nervous system is always present and frequently vagatonia though this may be marked. The combination of exophthalmic goiter and hypothyroidism is theoretically impossible and seems never to have been seen. Carbohydrate metabolism is commonly disturbed. The clinical forms of the disorder are very numerous. Thyro-endocrine associations are lacking in definitiveness. Drug therapy except iodine gives inconstant results.—R. G. H.

The diazo-reaction of thyroxin and its inhibition by constituents of the blood (Diazoreaktion des Thyroxins und ihre Hemmung durch Blutbestandteile). Komant, W., Arch. f. exper. Path. u. Pharmakol. **158**: 116. 1930. Abst., Chem. Absts. **25**: 3674.

Serum protein, uric acid and amino acids inhibit the diazo-reaction given by thyroxin with the diazonium salt of sulfanilic acid. Presumably this is due to a combination of the hormone with these substances. Thyroxin can apparently also combine with methylene blue or methyl violet. Despite the inhibition of the diazo-reaction, the mixture of thyroxin with serum, uric acid, etc., does not affect its property of increasing the gas metabolism of rabbits upon intravenous injection.

Does the hormone of the thyroid gland pass into the mother's milk? Lukacs, J., Magyar orvosi arch. **32**: 147. 1931. Abst., Chem. Absts. **25**: 3716.

In earlier work it was shown that experimental hyperthyreosis reduces the growth of rats, in proportion to the hyperthyreosis produced. On the basis of these results hyperthyreosis was produced in suckling mother rats by feeding them thyroid gland. Weight curves of the young rats were compared with those of control animals. The young of the hyperthyroidized mother rats were

retarded in their growth 31-34%, which shows that the thyroid hormone passes into the milk and increases or decreases in it according to changes of the hormone in the mother's organism.

The syndrome developing after simultaneous removal of the thyroids, parathyroids, and testes. Survival time and changes in blood chemistry (Sur le syndrome se développant après ablation simultanée expérimentale de la thyroide, des parathyroides et des testicules. Durée de survie et modifications chimiques du sang). Parhon, C. I. and H. Derevici, Compt. rend. Soc. de biol. **104:** 441. 1930.

In 10 dogs blood sugar was reduced by castration and increased by thyroparathyroidectomy, either with or without castration. Calcium was increased by castration and reduced under the other conditions. Cholesterine is increased in all the animals. No favorable effect of castration on the survival time of dogs following thyroparathyroidectomy could be observed.—J. C. D.

Brain phosphorous in experimental hyperthyroidism (Sur la teneur en phosphore du cerveau dans l'hyperthyroidie expérimentale). Parhon, C. I. and G. Werner, Compt. rend. Soc. de biol. **104:** 443. 1930.

Nine guinea pigs were fed powdered thyroid and one rabbit was injected with thyroxin. Compared with controls, there was an increase in brain and spinal cord phosphorous.—J. C. D.

The tachycardia of experimental hyperthyroidism. Priestley, J. T., J. Markowitz and F. C. Mann, Am. J. Physiol. **98:** 357. 1931.

It was shown that the heart rate of perfused hearts of thyroxinized rabbits and the heart-lung preparation of thyroxinized dogs is considerably greater than normal. Similarly, when the heart of a small dog is transplanted into the neck of a large dog by means of anastomosis of blood vessels the administration of thyroxin evokes definite tachycardia of the transplanted heart. It appears that the tachycardia of experimental hyperthyroidism is not dependent on the central nervous system, but on a peripheral mechanism.

—Authors' Summary.

The symptomatology of hypothyroidism. Starns, C. E., U. S. Vet. Bur. M. Bull. **7:** 564. 1931.

Starns from his study of numerous cases reported in the literature and those cases he has personally observed, concludes that the symptoms of myxoedema promptly suggest its diagnosis, but that the symptoms in the milder forms of hypothyroidism are less characteristic. He is convinced that when a patient who has a low metabolic rate complains of a tired, worn-out feeling, loss of strength, nervousness, vague pains and similar symptoms which cannot be readily accounted for, the possibility of hypothyroidism should be seriously considered.—Author's Abst.

Exophthalmic goiter. The development of refractoriness to iodine. Thompson, W. O. and Phebe K. Thompson, Arch. Int. Med. **48:** 351. 1931.

During the prolonged continuous administration of iodine one patient with exophthalmic goiter, after showing a remission, became completely refractory to 6 mgm. of iodine daily, a dose that was at other times sufficient to produce a maximum reduction in the basal metabolism. Four other patients became at least partially refractory to iodine during its prolonged administration in doses of from 6 mgm. to 250 mgm. daily. In four of the preceding five cases, iodine was omitted and the refractoriness disappeared. The fifth patient was operated on when the metabolism was rising rapidly during the continuous administration of iodine, and he died about forty hours afterward from a typical postoperative crisis. This reaction was indistinguishable from those previously seen in patients who were operated on without receiving iodine. The exact length of time necessary for the refractoriness to disappear completely when iodine is omitted is unknown; it was observed to do so within twenty-four days. When the metabolism reached its highest point during the administration of iodine, the disease was more severe than it had previously been, and all the peculiar nervous manifestations not only were present, but were more intense. In two patients, exophthalmos was first noted as the rate

of metabolism was rising during the continuous administration of small doses of iodine, and in the other two, it became more marked under these circumstances. Reactions appear to be more characteristic of severe cases than of mild cases. Our observations do not appear to support the hypothesis that the peculiar nervous manifestations of exophthalmic goiter are always under control as long as an excess of iodine is being administered. In severe cases operation should be performed as soon as a maximum reduction in the rate of basal metabolism occurs. In any case, when the metabolism has increased markedly during the administration of iodine, it is probably wise to postpone operation until after this medication has been omitted for from three to four weeks, with the patient at rest in bed, to allow the refractoriness to disappear, and until the administration of iodine has been resumed. Certain phenomena that may be related to the development of refractoriness to treatment with iodine are described.—Authors' Summary.

The effect of thyroid extract on undernourished children. Topper, A., Am. J. Dis. Child. **41**: 1289. 1931.

The effect of thyroid extract was studied on 16 children who were mentally retarded or physically underdeveloped. There were no obvious endocrine defects. The extract in small doses increased the basal metabolic rate in 4 children with a subnormal rate but had no effect in identical dosage on 12 who had normal metabolism. An increase in height well above the expected normal was noted during the period of treatment. There was also accelerated development in teething and bone development. The author is in accord with Kendall's opinion that thyroid extract or thyroxin speeds metabolism in the direction in which it is going. The basal metabolic rate is not the only criterion of thyroid therapy.—M. B. G.

The tachycardia, time factor, survival period and seat of action of thyroxine in the perfused hearts of thyroxinized rabbits. Yater, W. M., Am. J. Physiol. **98**: 338. 1931.

Perfused hearts of acutely thyroxinized rabbits beat at a much faster rate than hearts of non-thyroxinized rabbits, as has also been demonstrated by K. K. Lewis and McEachern (1931) and by Priestley, Markowitz and Mann (1931). There is a latent period of about 2 days following intravenous injection of thyroxine before this acceleration is noted. As shown by serial perfusion experiments, the heart continues to beat at a very rapid rate for about 12 days and then returns to the normal rate in about 17 days after the injection. Within certain limits dosage does not seem to make much difference in regard to the degree of tachycardia. This probably means that the smallest dose used was maximal. The survival period of rabbits' hearts sufficiently thyroxinized to make them acutely strongly hyperthyroid is not significantly different from the survival period of non-thyroxinized rabbits' hearts. It has been noted in the experiments that the hearts of thyroxinized animals were more subject to attacks of arrhythmia and seemed to beat more vigorously than normal. After excision of the sino-auricular node of the perfused heart of the acutely thyroxinized rabbit, the heart rate is still greatly increased. When auriculoventricular dissociation is produced by crushing the bundle of His ventricles usually beat at an accelerated rate. These results mean that the auricles and ventricles independently beat faster than normally. Thyroxine seems to exert its effect, therefore, upon all parts of the heart. This study does not indicate whether the action of thyroxine is upon the muscle fibers or upon the nerve endings in the myocardium, but other studies now being made (Cecile Markowitz) give reason to believe that it is directly upon the muscle cells.—Author's Summary.

Thyroidectomy and pancreatic diabetes (Thyroidectomie et diabète pancréatique). Yriart, M., Compt rend. Soc. de biol. **105**: 128. 1930.

Only dogs in good health after the operations were used. The parathyroids were left in place. Five series were used: (1) animals pancreatectomized after thyroidectomy, (2) animals thyroidectomized after sub-total pancreatectomy, (3) animals in which the sugar curve produced by the injection of glucose was followed before and after injection of thyroid, (5) diabetic animals hyperthyroidized. The thyroid did not modify carbohydrate metabolism as tested in any of the above ways.—J. C. D.